Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds Promoted by Nickel Nanoparticles

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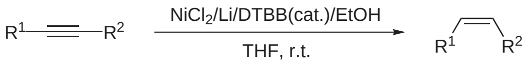
Dedicated to Professor Richard Heck for his pivotal contribution to the transition-metal-catalyzed reactions

Abstract: The system composed of nickel(II) chloride, lithium metal, a catalytic polymer-supported arene, and ethanol, has been efficiently applied to the conjugate reduction of a variety of α,β-unsaturated carbonyl compounds (ketones and carboxylic acid derivatives) under very mild reaction conditions.

Key words: conjugate reduction, ketones, carboxylic acid derivatives, nickel, nanoparticles

The conjugate reduction of α,β-unsaturated carbonyl compounds is an important functional group transformation in organic synthesis.[1,2] Most of the attention has been devoted, however, to the chemoselective reduction of α,β-unsaturated ketones.[2,3] Some general methods for the partial reduction of enones include electron-transfer reduction, catalytic and transfer hydrogenation, metal hydrides or biochemical reductions.[2] Among them, copper(I) hydride mediated reductions have shown to be very effective for this purpose and have been widely studied.[4] Nickel-based reducing agents, such as the complex reducing agent NiCRA,[5] ultrasonically activated Zn–$NiCl_2$[6] or Raney nickel,[7] have also found application in this transformation. In a more recent study, nickel boride,[8] generated in situ from $NiCl_2\cdot 6H_2O$ and $NaBH_4$ in methanol–water, chemoselectively reduced a variety of α,β-unsaturated carbonyl compounds.[9] However, the large amounts of $NiCl_2\cdot 6H_2O$ used (and also of $NaBH_4$, 1:5–1:30 substrate/Ni molar ratio, i.e. 1.19 g to 7.31 g of nickel salt per mmol of substrate) clearly curtail the application of this methodology. At any rate, the 1,4-selective reduction of carboxylic acid derivatives has not been developed as much as that of ketones and aldehydes.[8,10]

On the other hand, we have recently reported the fast synthesis of nickel(0) nanoparticles with diameters of 2.5±1.5 nm by reduction of anhydrous nickel(II) chloride with lithium powder and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl) in tetrahydrofuran at room temperature.[11] The high reactivity of these nanoparticles was demonstrated in the catalytic hydrogenation of a variety of organic compounds.[12,13] Moreover, similar reduction systems to $NiCl_2$/Li/DTBB(cat.) such as $NiCl_2$/Li/copolymer(cat.),[13] $NiCl_2\cdot 2H_2O$/Li/DTBB(cat.),[13] $NiCl_2$/Li/DTBB(cat.)/EtOH, or $NiCl_2$/Li/copolymer(cat.)/EtOH, also generate nanosized metallic nickel[14] with demonstrated or potential applicability in organic chemistry. Very recently, we have discovered that the introduction of an alcohol (EtOH or *i*-PrOH) as a source of hydrogen in the reducing system [i.e., $NiCl_2$/Li/DTBB(cat.)/ROH] is a very convenient method for the highly stereoselective *cis* semi-hydrogenation of internal alkynes (Scheme 1) and the semi-hydrogenation of terminal alkynes under mild reaction conditions.[15]



Scheme 1

We want herein to introduce a variant of the above-mentioned reducing system and its application to the selective conjugate reduction of a variety of α,β-unsaturated compounds. In this case, a polymer-supported arene,[12b,16] prepared by radical copolymerisation of 4-vinylbiphenyl and divinylbenzene (mixture of regioisomers),[16b] was utilised as an electron carrier instead of DTBB. As a result, easier workup was achieved, since the arene is removed by simple filtration, and cleaner reaction crudes were obtained in all cases.

The role of the different components of the reducing system mentioned above is as follows: (a) nickel(II) chloride is the source of Ni(0) nanoparticles, (b) lithium has got a double role, the reduction of Ni(II) to Ni(0) and the in situ generation of molecular hydrogen by reaction with ethanol, (c) the polymer-supported arene is used in catalytic amounts and acts as an electron carrier from lithium to nickel(II) chloride, and (d) ethanol is the source of hydrogen. One of the main advantages of this methodology is that the handling of external molecular hydrogen is avoided since it is generated in situ in the reaction flask. In this letter, this reducing system has been successfully applied to the selective 1,4-reduction of a variety of unsaturated ketones and carboxylic acid derivatives in tetrahydrofuran at 0 °C or room temperature (Scheme 2).[17,18]

Concerning the reduction of acyclic α,β-unsaturated ketones, chalcone was mildly reduced in very high isolated yield (Table 1, entry 1). By adding 1.8 mmol excess of both lithium metal and ethanol, phorone was transformed

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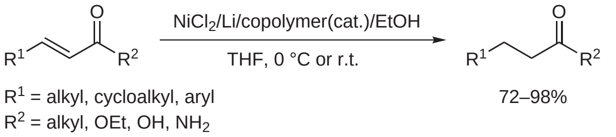

Scheme 2

into diisobutylketone as a result of the effective reduction of the two carbon–carbon double bonds (Table 1, entry 2). The 1,4-reduction was also selective for ketones containing an additional endocyclic carbon–carbon double bond, either an isolated or a conjugated one. Thus, both α- and β-ionone were reduced to the expected products in good yields and without any double bond isomerisation (Table 1, entries 3 and 4).

Monocyclic and bicyclic unsaturated ketones, such as isophorone and (1*S*)-verbenone, respectively, were also reduced in high isolated yields at room temperature and in shorter reaction times in comparison with the acyclic ketones (Table 1, entries 5 and 6). The exocyclic conjugated carbon–carbon double bond of (*R*)-(+)-pulegone, even though tetrasubstituted, was reduced with a high yield to give a *cis*/*trans* (75:25) diastereomeric mixture of (+)-isomenthone and (–)-menthone, respectively (Table 1, entry 7). More challenging was the reduction of (*R*)-(–)-carvone, which contains a conjugated trisubstituted carbon–carbon double and an isolated methylidene group (Table 1, entry 8). In this case, the reduction showed to be regioselective, the conjugate reduction being more favoured furnishing a *cis*/*trans* (83:17) diastereomeric mixture of (+)-isodihydrocarvone and (+)-dihydrocarvone, respectively, in 82% yield. Nonetheless, in this case a 18% yield of the overreduced ketone *p*-menthan-2-one was observed.

This methodology was also applied to the selective reduction of several α,β-unsaturated esters, which proceeded, in general, faster than that of ketones. For instance, ethyl *trans*-crotonate and ethyl cinnamate were reduced at room temperature in only 1.5 hours and 3 hours, giving ethyl butyrate and ethyl hydrocinnamate, respectively, in 98% yield (Table 1, entries 9 and 10). Similarly, diethyl maleate was reduced to diethyl succinate in 5 hours and 92% isolated yield (Table 1, entry 11).

Finally, we explored the possibility to extend this reducing system to other carboxylic acid derivatives. Both cinnamic acid and cinnamamide were selectively reduced under the same conditions giving high yields of hydrocinnamic acid and hydrocinnamamide, respectively (Table 1, entries 12 and 13). In these cases, the reactions proceeded slower in comparison with the rest of the substrates studied in this letter.

It is noteworthy that the conjugate reduction of other α,β-unsaturated compounds, such as aldehydes or nitriles, under the conditions depicted in Scheme 1 was not so effective. Nonetheless, the conjugate reduction of the carbon–carbon bond of a α,β-enal is inherently more difficult than that of an enone because of the greater reactivity of the aldehyde functionality. At present, we are trying to optimise the reaction conditions in order to broaden the substrate scope of this methodology.

In conclusion, we have described a new reducing system, based on the in situ generation of nickel(0) nanoparticles and molecular hydrogen, which has been successfully applied to the selective conjugate reduction of α,β-unsaturated ketones and carboxylic acid derivatives. Good to excellent yields of the products were obtained under very mild reaction conditions.

Acknowledgment

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References and Notes

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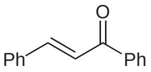
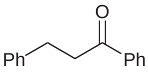
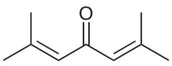
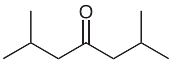
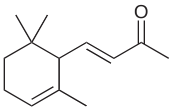
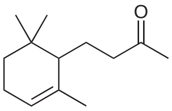
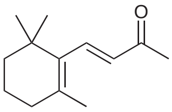
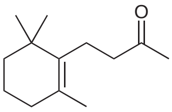
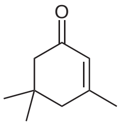
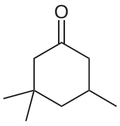
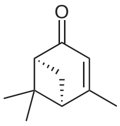
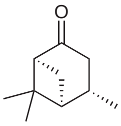
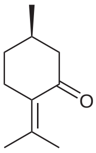
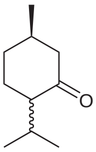
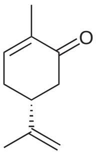
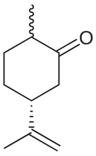
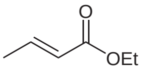
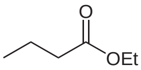
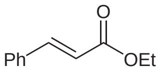
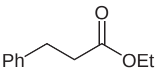
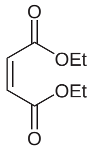
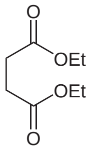
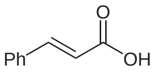
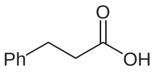
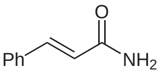
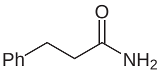
Table 1 Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds

Entry	Substrate	Temp (°C)	Time (h)	Product	Yields (%)[a]
1		0	12		95[b]
2		r.t.[c]	12		91
3		0	12		72[b]
4		0	12		75[b]
5		r.t.	5		92[b]
6		r.t.	4		92
7		0	8		91[d]
8		0	16		82[e,f]
9		r.t.	1.5		98[e]
10		r.t.	3		98
11		r.t.	5		92
12		r.t.	24		92
13		r.t.	24		93[g]

[a] Isolated yield from the reaction crude, unless otherwise stated.

[b] Isolated yield after column chromatography (flash silica gel, hexane–EtOAc).

[c] Following the general procedure (ref.[13]) but using Li (42 mg, 6 mmol) and EtOH (0.23 mL, 4 mmol).

[d] Obtained as a *cis*/*trans* (75:25) diastereomeric mixture.

[e] GLC yield.

[f] Obtained as a *cis*/*trans* (83:17) diastereomeric mixture.

[g] Isolated yield after recrystallisation in Et_2O.

(17) The products 1,3-diphenylpropane-1-one, diisobutylketone, 3,3,5-trimethylcyclohexanone, (+)-dihydrocarvone, (–)-menthone, (+)-isomenthone, ethyl butyrate, ethyl hydrocinnamate, ethyl succinate, and hydrocinnamic acid, were characterised by comparison of their chromatographic and spectral data with those of the corresponding commercially available pure samples. Dihydro-α-ionone,[19] dihydro-β-ionone,[20], dihydroverbenone,[21] (+)-isodihydrocarvone,[22] *p*-menthan-2-one,[22], and hydrocinnamamide,[23] were characterised by comparison of their chromatographic and spectral data with those described in the literature.

(18) **General Procedure for the Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds**: Anhyd $NiCl_2$ (130 mg, 1 mmol) was added to a suspension of Li powder (29.4 mg, 4.2 mmol) and the vinylbiphenyl–divinylbenzene copolymer (52 mg, 0.05 mmol) in THF (2 mL) under an Ar atmosphere. After 10 min, a black suspension was formed indicating the generation of the nickel(0) nanoparticles. The suspension was diluted with THF (18 mL) followed by the addition of EtOH (0.13 mL, 2.2 mmol) and the substrate (1 mmol). The reaction course was monitored by GC–MS until the complete disappearance of the starting material. The resulting mixture was filtered through a pad containing celite (upper layer) and silica gel (lower layer) in a 3:1 ratio, dried over anhyd Na_2SO_4, and the solvent was evaporated under vacuum (15 Torr). Most of the reaction crudes did not need any further purification, whereas in some cases purification by column chromatography was applied (see footnotes in Table 1).

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