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Utility of Neodymium Diiodide as a Reductant in Ketone Coupling Reactions

William J. Evans,* Penny S. Workman, and Nathan T. Allen

*Department of Chemistry, University of California−Irvine,
Irvine, California 92697-2025*

wevans@uci.edu

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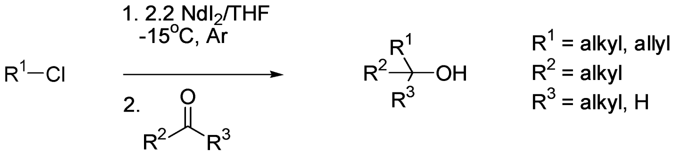
ABSTRACT



The viability of NdI_2 as a one-electron reducing agent in organic synthesis has been examined by studying coupling reactions between alkyl chlorides and ketones and aldehydes.

For many years, samarium diiodide has been a standard one-electron reductant in organic synthesis.[1−4] It is broadly useful, and its reduction potential can be enhanced by addition of hexamethylphosphoramide (HMPA).[5] Recently, there have been rapid advances in the availability of more powerful divalent lanthanide reducing agents useful for organic synthesis. The 1997 discovery of the first molecular complex of Tm(II)[6] prompted the development of TmI_2 as an alternative for the commonly used $SmI_2(THF)_x$/HMPA combination.[5] This Tm(II) reagent can effect more difficult reductions than Sm(II)/HMPA and avoids the carcinogenicity of HMPA. For example, it allows ketone−alkyl halide couplings to be accomplished with chlorides even at low temperatures.[7]

The isolation of the first molecular complex of Dy(II)[8] provided an even more powerful reductant[9] that can also accomplish useful organic transformations.[8] Hence, even though it initially appeared that Tm(II) and Dy(II) were too strongly reducing to exhibit useful synthetic reductive chemistry in solution, these systems have proven to be viable.[7,8]

The existence of Nd(II), an even more reducing divalent lanthanide, as a soluble molecular species was recently established by Bochkarev et al.[10] It was uncertain if Nd(II), which has a Ln(III)/Ln(II) reduction potential vs NHE of −2.6 V compared to Sm (−1.55 V), Tm (−2.3 V), and Dy (−2.5 V),[9] would be viable as a synthetic reagent. We report here that NdI_2 can be used as a lanthanide reducing agent in organic synthesis. In addition to being more reducing, NdI_2 may offer some special advantages over the other divalent lanthanide halide reagents. It is cheaper and has a larger radial size, which can be important in optimizing lanthanide reaction chemistry.

NdI_2 can be generated in 40 g (100 mmol) quantities by direct reaction of metal and iodine at 600 °C.[11] This solid can be stored for months at room temperature in the absence of solvent. Solutions are stable under an argon atmosphere[12]

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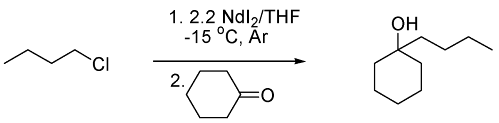
Table 1. Reductive Coupling of Cyclohexanone with Alkyl Chlorides Using NdI_2 in THF

alkyl chloride	% yield (GC, based on unreacted ketone)
n-butyl chloride	97
sec-butyl chloride	99
tert-butyl chloride	0
phenethyl chloride	81

for several hours at −15 °C but decompose over a period of minutes at room temperature. Hence, NdI_2 must be used quickly once it is put in solution and reactions must be performed at subambient temperatures.

Although NdI_2 is more reactive than the other LnI_2 reagents, its high reactivity actually leads to a simpler experimental protocol. Since the reagent is best stored as a solid and solutions are used immediately, the problem of solutions changing concentration over time is avoided. A standardized solution, typically 0.05 M at −15 °C, can be produced and transferred via a syringe to a flask containing the substrate to be reduced.[13] The reactions are run at low temperatures and are often complete upon mixing.

The first set of transformations examined with $NdI_2(THF)_x$ were ketone coupling reactions with alkyl halides, since the results could be directly compared with those for SmI_2,[14,15] TmI_2,[7] and DyI_2.[8] Addition of 1-chlorobutane to a solution of $NdI_2(THF)_x$ at −15 °C immediately dissipated the purple color to form a light green intermediate. After reaction with cyclohexanone, a 97% (GC) yield of the coupled product, 1-butylcyclohexanol, was obtained following aqueous workup (eq 1). Other chlorides may also be reduced in a similar manner, as shown in Table 1. It was found that reaction of primary and secondary chlorides proceeds in good yield. No reaction occurs, however, when a tertiary chloride is used.



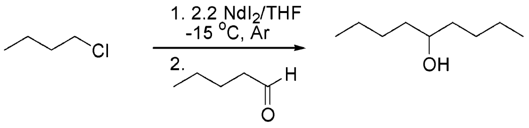
(1)

Table 2. Reductive Coupling of 2-Hexanone with Alkyl Chlorides Using NdI_2 in THF

alkyl chloride	% yield (GC, based on unreacted ketone)
n-butyl chloride	100
sec-butyl chloride	77
tert-butyl chloride	0
phenethyl chloride	81
allyl chloride	82

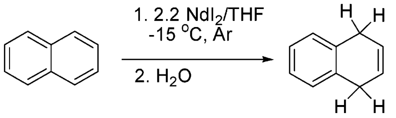
Similar results were obtained using the noncyclic ketone, 2-hexanone, as shown in Table 2.

NdI_2 coupling of an alkyl halide with an aldehyde substrate was also examined. The coupling of 1-chlorobutane with valeraldehyde gave the coupled alcohol, 5-nonanol in 93% yield (eq 2).



(2)

NdI_2 in THF has also been found to reduce naphthalene. Reaction of 2.2 equiv of NdI_2 with naphthalene forms an intense blue solution, which after hydrolysis yields dihydronaphthalene (eq 3), i.e., it has Birch reduction-type reactivity.



(3)

In conclusion, these preliminary results show that NdI_2 is not too reactive to be useful as a reductant in organic synthesis. Hence, NdI_2 can join TmI_2 and DyI_2 in bridging the gap in available reductants with reduction potentials between those of SmI_2/HMPA and alkali metal/liquid ammonia Birch reductants. It is anticipated that NdI_2 will develop into a broadly useful reagent, just as SmI_2 has developed over the past 20 years.[1−4]

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[12] We have found that the presence of dinitrogen substantially reduces the stability of solutions, even at −30 °C.

[13] **General Method for Using $NdI_2(THF)_x$.** A septum-capped flask was charged with black NdI_2 (1.0 g, 2.5 mmol) and a stir bar under argon. The flask was placed in a −15 °C 2-propanol/ice bath. Precooled THF (45 mL, −15 °C) was added via cannula, immediately producing a purple solution. The solution was stirred for 45 min. An aliquot of the saturated solution was removed and its concentration determined to be 0.05 M by complexometric titration.[7] An aliquot (24.0 mL, 1.2 mmol) was added via syringe to a septum-covered flask under argon at −15 °C. Subsequently, the organic halide (0.55 mmol) was added via syringe. Once a green solution was formed, the ketone (0.50 mmol) was added via syringe, resulting in a light blue solution. The reaction was then quenched with a saturated solution of NH_4Cl and extracted with ether or pentanes. The organic extract was washed with H_2O (2 × 10 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to yield the coupled product.

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