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Complex intermediates in the NO insertion reactions into lithium amides†

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ABSTRACT: Nitric oxide (NO) is known to produce the carcinogenetic nitrosamines but it has also been recently reported, both as a regulator of many important physiological functions and as a possible pharmaceutical delivery system. The present paper describes the NO insertion into N—Li bond of lithium amides, to afford very good to almost quantitative yields of *N*-nitrosamines. A study of the reaction intermediate suggested a further advantage of this synthetic methodology, widening its scope to its use in tandem reactions. Thus, *in situ* addition of an organolithium reagent into the N═O bond leads to an almost quantitative conversion into the corresponding hydrazone. This compound could further add a second equivalent of the same (or another) organolithium affording substituted hydrazines. The hydrazines thus prepared have a potential chiral carbon, by running the reaction in the presence of a chiral auxiliary, enantiomeric excess could be obtained. By reducing the compound with Raney Ni, the scope of this methology could be enlarged for the potential preparation of chiral primary amines, project that is currently under progress. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: nitrosamines; lithium amides; NO insertion; tandem reactions; hydrazones

INTRODUCTION

Nitrosation of amines and of DNA by nitrosamines is a well known carcinogenetic effect;[1,2] a recent study investigated nitric oxide (NO)-mediated nitrosation of 2-amino-3,8-dimethylimidazo-4,5-*f*]quinoxaline and the influence of dietary (hemin) and inflammatory [NO, myeloperoxidase, and H_2O_2] components on nitrosation.[3] Nevertheless, a new and unexpected role of nitric oxide (NO) has been recently reported, both as a regulator of many important physiological functions *in vivo* and as a possible pharmaceutical delivery system.[4,5] In spite of the increased interest in nitrosamines, there are few reported procedures for their synthesis with good yields;[6,7] a recent approach describes a combined solid/solution-phase methodology that enables the efficient synthesis of some individual nitrosamines as well as mixture-based nitrosamines libraries.[4] We recently reported a preliminary synthetic procedure based on the NO insertion into N—Li bond of lithium amides, that afforded an almost quantitative yield of di-cyclohexylnitrosamine.[8] In the present paper, we describe further research on the subject looking for reaction intermediates that could be used in tandem reactions.

The synthetic strategies, known as 'tandem,' 'domino,' or 'cascade reactions' combine several transformations, often incorporating added components.[9] A very important advantage of these synthetic procedures is the minimization of waste, since several bonds could be formed in one sequence without isolating the intermediates or changing the reaction conditions,[10] the amounts of solvents, reagents, adsorbents and energy is dramatically decreased, compared with stepwise reactions.[11] The design of tandem reactions involving organometallic compounds combines the mentioned advantages with the versatility of organometallic reagents, we have recently published two reviews related to tandem reactions involving organolithium intermediates.[12]

RESULTS AND DISCUSSION

Reaction of lithium amides with NO

This reaction constitutes a very convenient methodology for the synthesis of alkyl *N*-nitrosamines, **3**, from

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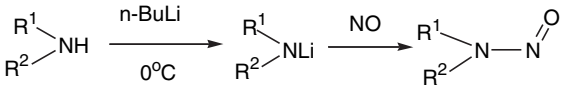
amines, **1**, by nitrosation of lithium amides, **2**, [Eqn (1)].



1 **2** **3**

a: $R^1 = R^2 = c\text{-}(C_6H_{11})$

b: $R^1 = i\text{-}C_3H_7$; $R^2 = c\text{-}(C_6H_{11})$

(1)

The NO insertion into the N—Li bond described herewith, afforded almost a quantitative yield of *N*-nitrosodicyclohexylamine, **3a**, and near 80% yield of *N*-nitrosoisopropylcyclohexylamine, **3b**. The reaction can be carried out under mild conditions: in THF at low temperature (−78 or 0°C) and atmospheric pressure, (ca. 1013 bar) giving only one product. It was initially carried out using a cylinder of NO,[8] but due to the present difficulties for importing NO, it was desirable to try methods for the preparation of NO at atmospheric pressures, and test the methodology under these conditions. Optimization of the NO preparation as described in the experimental section, afforded almost the same yields of **3a** and **3b** stated above.

It is known, that lithium dialkylamides exhibit large structural varieties and this fact has generated a persistent debate about the relative reactivity of different aggregation states.[13] An enormous body of structural investigations, mostly crystallographic[14] and spectroscopic,[15] has been accumulated in the last years. Concomitantly with the experimental investigations many detailed computational studies of aggregates of lithium dialkylamides have been carried out by using *ab initio* and/or semiempirical methods[16–18] with variable degrees of accuracy, according to the size and nature of the systems examined. On the other hand, we have recently demonstrated that lithium amides formed from cyclic amines (such as piperidine) formed mixed aggregates with the precursors amine,[19] while lithium amides formed from open dialkyl amines forms homodimers.[20] Nevertheless, for the sake of simplicity, in Eqn (1), and the following equations, **2** is written as monomer.

To get good yields of *N*-nitrosamines, the preparation of the lithium dialkylamide has to be carried out with a slight excess of the corresponding amine; if BuLi is in excess addition to the double bond of **3**, could occur under the reaction conditions, as shown by Eqn (2).

This observation led us to develop a new methodology for the tandem preparation of substituted hydrazones, **4**, and hydrazines, **5** in very good to excellent yields**.** Thus, starting from **1a**, transforming it into **2a** and carrying out the reaction with NO in the presence of 2 equivalents of BuLi, and almost quantitative conversion of **1a** into **4a**, was obtained without isolation of the corresponding **3a**. If the reaction is carried out in a great excess of BuLi (3–4 equivalents) a 70% of the corresponding hydrazine, **5a**, ($R^3 = CH(CH_2)_2CH_3$) was obtained.

The methodology is quite general: by carrying out the reaction in the presence of second equivalent of BuLi, and, without isolating the intermediate adding *n*-$C_5H_{11}Li$ the corresponding **5** ($R^3 = C_5H_{11}$) is obtained in good yield (ca. 70%). It is worth mentioning that **5** exhibits an asymmetric C atom; therefore, by carrying out the addition of the second organolithium reagent in the presence of a chiral auxiliary, enantioselective formation of **5** could be obtained. Examination of the scope of this step is under progress.

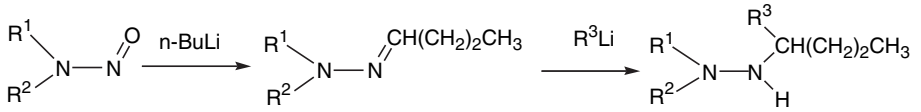
Reaction intermediate

It was of interest to make some contribution toward the understanding of the mechanism of the insertion reaction of NO into the N—Li bond. Therefore, a ^{13}C NMR examination of the reaction mixture of the lithium dicyclohexylamide with NO in THF was carried out under the conditions that led to the complete conversion to **3a**. Table 1 gathers the significant signals for the dicyclohexylamine, **1a**, the lithium dicyclohexylamide, **2a**, the *N*-nitrosamine **3a** and the reaction mixture.

It can be observed that the reaction mixture shows distinctive signals. The ^{13}C NMR of the reaction mixture at $t = 0$, at 0°C, shows the signals for **2a**, while at $t = 60$ min

Table 1. ^{13}C NMR of the dicyclohexylamine **1a**, lithium dicyclohexylamide **2a**, *N*-nitrosamine **3a**, and the reaction mixture

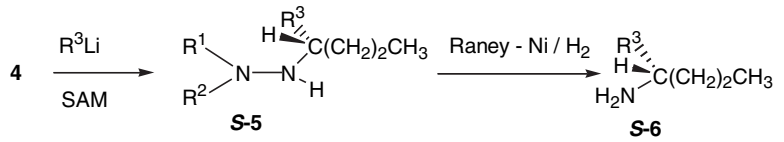
Compound	C_1	C_2	C_3	C_4
1a	53.2	34.9	26.8	25.4
2a	62.3	40.1	27.6	27.6
3a	60.10/54.61	35.42/30.16	26.9/26.7	26.4/26.35
Reaction mixture	58.4	35.1	29.8	26.6



3 **4** **5**

(2)

no signals for **1a**, nor **3a** were observed, some **2a** remained unreacted and the new signals shown in Table 1 appeared. As it is well known, NO is paramagnetic, nevertheless the ^{13}C NMR shows sharp signals. We believe that a dimeric form of the nitrosamine lithiated precursor might be involved; nevertheless further insight into the mechanism of this useful reaction is needed.



(3)

It has been recently reported a convenient methodology for the synthesis of chiral primary amines starting from hydrazones, producing hydrazines in the presence of a chiral inductor (SAM/RAM procedure).[21] Hydrazines **5** obtained from amines according to the methodologies shown by Eqns (1)–(3), prepared in the presence of a chiral auxiliary, could then be reduced by Raney Ni, affording new chiral primary amines. Therefore, the herewith-described methodology could be enlarged to a tandem sequence for the enantioselective preparation of chiral primary amines [Eqn (3)]. Examination of this step is under progress.

EXPERIMENTAL SECTION

General comments

CAUTION: NO is dangerous; use of an efficient hood and protecting shield is essential. N-nitrosamines are carcinogenic; they have to be handled and disposed with special care avoiding skin contact. All reactions involving organolithium reagents were carried out by standard techniques for the manipulation of air- and water-sensitive compounds.[22] The GLC analyses were carried out on a 5890 Series II Plus Hewlett-Packard (using a HP-5 column) gas chromatograph, at 60–250°C programmed temperature. Mass spectra were recorded on a BG Trio-2 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in a Brucker 200 MHz.

Solvents and reagents

Distilled THF was refluxed over sodium benzophenone ketyl until a dark blue solution was obtained and then distilled immediately before use under dry oxygen-free nitrogen. Hexane was treated in a similar way. Commercial dicyclohexylamine and isopropylcyclohexylamine were separately left over sodium strings for several days, refluxed and distilled over sodium, they were then kept under nitrogen in sealed ampoules, which were opened immediately prior to use. *n*-Butyllithium was prepared as previously described.[23] Several methods were tested to generate NO; the best results were obtained by the reported method using ferrous sulfate and sodium nitrite solutions.[24]

Preparation of lithium dialkylamides

Cooled (0°C) *n*-BuLi (5 mL, 0.8 M in hexane) was syringed into a non-air stopper capped tube under nitrogen atmosphere, and freshly distilled dicyclohexylamine (7.4 mmol) was added. The precipitate lithium dicyclohexylamide was centrifugated, the supernatant removed, and the white crystals were washed thrice with 5 mL of hexane followed by centrifugation each time. The resulting solid was dried under vacuum at room temperature. Atmospheric pressure was restored by flushing with dry, oxygen-free nitrogen. Lithium isopropylcyclohexylamide was prepared in a similar way but, since it is soluble in hexane, the solvent was distilled at reduced pressure until the total volume left was nearly 1.5–2 times the volume of the added amine. The resulting syrup was dissolved in THF and used immediately. Both lithium amides were titrated as previously described.[25]

Reaction between lithium dialkylamides and NO

Typical reaction conditions are described for lithiumdicyclohexylamide. A 100 mL round-bottomed flask containing a teflon-coated stirring bar and capped with a no-air stopper was evacuated and filled with dry nitrogen alternatively several times, and then nitric oxide was added at ca. 1013 mbar. After that the flask was put into an ice-water bath, and a solution of lithium dicyclohexylamide (1 mmol) in anhydrous THF (4 mL) was added at once under vigorous magnetic stirring, that was kept for 3 h. The initial colorless solution turned to orange at the beginning of the reaction and this color stayed along the reaction. The reaction was worked up by treating the reaction mixture with 0.2 mL of distilled methanol. Excess NO was removed and distilling the THF under reduced pressure afforded slightly orange crystals of *N*-nitrosodicyclohexylamine, in an almost quantitative

yield. Crystallization from ethanol–water rendered white crystals, m.p. 104.5–105.5°C. The *N*-nitrosoisopropylcyclohexylamine was obtained in a similar way. Both nitrosamines were fully characterized by mass spectrometry, ^{1}H- and ^{13}C-NMR spectroscopy.

Preparation of hydrazones

For the preparation of *N-i*-propylcyclohexyl-hydrazobutanone, the methodology described for the preparation of lithium amides was used but using 15 mL of Bu Li (0.8 M in hexane) instead of 5 mL. The rest of the procedure is similar, as well as the reaction of the resulting lithium *i*-propylcyclohexylamide with NO. The reaction mixture was worked up as described above. The *N-i*-propylcyclohexyl-hydrazo-butanone was isolated as an orange oil by preparative TLC (using hexane-ethyl acetate 3:2 as eluent). The same compound was independently obtained by treating the isolated the *N-i*-propylcyclohexylnitrosamine with Bu Li.

Similarly, the 4-(*N*-dicylohexyl)hydrazine-octane was obtained in a 70% yield by using 25 mL instead of 5 mL, for the preparation of the *N*-dicylohexyl lithium amide. Optimization of the reaction conditions, isolation and full characterization of these compounds is under progress.

N-dicyclohexylnitrosamine, **3a.** Melting point: 104.5–105.5°C. ^{1}H-NMR ($CDCl_3$) (ppm): 1.60 (m, 20H), 3.73 (m, 1H), 4.84 (m, 1H). ^{13}C-NMR ($CDCl_3$) (ppm): 26.36, 26.41, 26.66, 26.90, 30.16, 35.42, 54.61, 60.10. MS *m/e* (rel. int.): 210 (6.96), 129 (7.28), 98 (12.83), 83 (100.00), 67 (12.72), 55 (61.74), 41 (42.17).

N-cyclohexy-i-propylnitrosamine, **3b.** ^{1}H-NMR ($CDCl_3$) (ppm): 1.16 (d), 1.51 (d), 1.6 (m), 3.75 (m, 2H), 4.23 (m, 1H), 4.80 (m, 1H), 5.05 (m, 2H). ^{13}C-NMR ($CDCl_3$) (ppm): 19.05, 23.77, 25.18, 25.32, 25.48, 25.97, 29.20, 34.10, 44.72, 50.85, 52.70, 58.47.

N-cyclohexy-i-propyl-butylhydrazone, **4b.** ^{1}H-NMR ($CDCl_3$) (ppm): 0.94 (t, 3H), 1.07 (d, 6H), 1.47 (m, 12 H), 2.20 (m, 2H); 3.07 (m, 1H), 3.58 (m, 1H), 6.88 (t, 1H). ^{13}C-NMR ($CDCl_3$) (ppm): 13.80, 20.29, 20.80, 26.11, 30.86, 31.02, 35.20, 47.70, 56.89, 141.01. MS *m/e* (rel.int.): 211 (38.21), 196 (60.85), 168 (83.96), 126 (56.13), 114.00 (100.00), 99 (11.91), 86 (16.16), 84 (20.40), 71 (26.06), 56 (68.40), 42 (70.75).

N-dicyclohexyl-butylhydrazone, **4a.** MS *m/e* (rel. int.): 250 (33.3), 207 (80.16), 167 (12.0), 138 (22.9), 125 (100), 110 (11.4), 98 (23.2), 83 (36.6), 69 (28.3), 56 (42.9), 55 (75.88).

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