Tetrahedron Letters,Vol.30,No.39,pp 5197-5200,1989	0040-4039/89 $3.00 + .00
Printed in Great Britain	Pergamon Press plc

ADDITION AND LITHIATION REACTIONS OF N-(1-PHENYLALKYLIDENE)ANILINES WITH LITHIUM DIALKYLAMIDES

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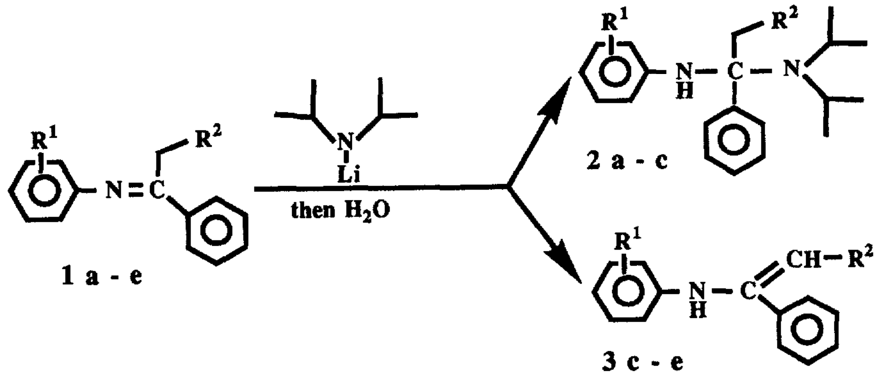
Summary. Lithium diisopropylamide undergoes an addition reaction to the methyleneamino moiety of the title Schiff's bases substituted with a cyano group at the *ortho* or *para* position of the aniline, but mediates tautomerization of the unsubstituted and *meta*-substituted derivatives into secondary enamines. Only the tautomerization is observed for lithium 2,2,6,6-tetramethylpiperidide-mediated reactions.

Lithium dialkylamides, including the most widely used lithium diisopropylamide (LDA), are a cornerstone of modern organic synthesis. The major applications of these sterically hindered bases involve kinetically-controlled proton abstractions.[2] Limited examples of other LDA-induced reactions have been reported recently.[3] It appears that LDA can act as the N-analogue in the Meerwein-Ponndorf-Verley reduction,[4] an efficient single electron donor to molecules with favorable reduction potentials,[5] and a nucleophile.[6] In this paper we report several new dialkylamide-mediated reactions of Schiff's bases **1**.



a R^1 = o - CN, R^2 = Me

b R^1 = o - CN, R^2 = i - Pr

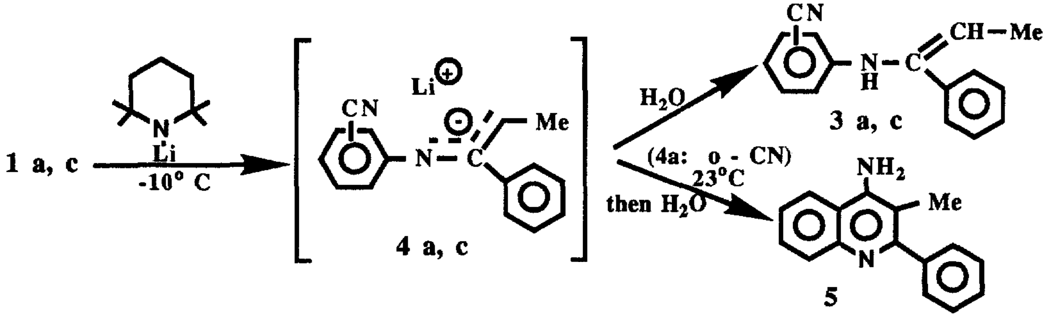
c R^1 = p - CN, R^2 = Me

d R^1 = m - CN, R^2 = Me

e R^1 = H, R^2 = Me

Recently we have described[7] an efficient synthesis of 4-aminoquinolines based on the lithiation reaction of Schiff's bases, such as **1** (R^1=*o*-CN, R^2=H), with LDA. For example, this derivative is lithiated at the methyl group by treatment with LDA, and the resultant anion undergoes an intramolecular addition reaction to the adjacent cyano group to give, after aqueous workup, 4-amino-2-phenylquinoline.

A similar treatment of the ethyl analogue **1a**[8] did not produce the expected 3-methylquinoline derivative. The only product isolated in a high yield from the mixture by chromatography was the adduct **2a**.[9,10] To understand better this unusual reaction, four additional Schiff's bases **1b**-**e**[8] were allowed to react with LDA.[9,10] A clean addition reaction with the more sterically hindered isobutyl derivative **1b** was observed. However, the reaction of *para*-cyano-substituted compound **1c** gave a mixture of adduct **2c** and secondary enamine **3c** in the ratio of 1:1. A similar treatment of *meta*-cyano derivative **1d** and the unsubstituted Schiff's base **1e** with LDA and followed by quenching the mixtures with water produced the respective secondary enamines **3d** and **3e** but not the addition products. These results show that the reactions of *ortho*- and *para*-cyano-substituted compounds with LDA must be regarded as formal 1,6- (for **1a** and **1b**) and 1,8-conjugate additions (for **1c**) with the participation of the cyano group. The 1,8-addition is expected to be less efficient than the 1,6-addition and, not surprisingly, is accompanied by a lithiation reaction. A kinetic protonation of the resultant anion produces an enamine. A conjugate addition is not possible for compounds **1d** and **1e** and, therefore, only the lithiation reaction is observed.



The formation of secondary enamines in the reactions mentioned above deserved a special attention because only a few examples of this class of compounds are known.[11] In most cases studied these enamines could not be isolated, and their presence in solution, as a result of the imine-enamine equilibrium, has only been indicated using spectroscopic methods.[11b,c] It appeared to us that the conjugate addition of an amide anion with *ortho*- and *para*-cyano-substituted Schiff's bases could be suppressed by the use of a more sterically hindered base, such as lithium 2,2,6,6-tetramethylpiperidide (LTMP). Indeed, both **1a** and **1c** were lithiated smoothly upon treatment with LTMP at -10°C. Quenching of the mixtures with water produced the respective secondary enamines **3a** and **3c**. Compound **3c** was contaminated slightly with polymeric materials. However, these were removed by a simple filtration of a crude solution through a thin layer of silica gel pretreated with triethylamine to give an analytically pure sample of **3c**.[12]

The secondary enamines **3** tautomerized rapidly to the corresponding imines **1** (thermodynamic products) upon treatment with a catalytic amount of acid, but showed a remarkable stability when stored under aprotic conditions. Thus, enamine **3e** had a half-life of a few hours at 0°C for both a neat sample and a solution in deuteriochloroform. The cyano-substituted compounds **3a**, **3c**, and **3d** showed no sign of isomerization upon storage for one week under similar conditions.

The efficient preparation of the *ortho*-cyano-substituted enamine **3a** at -10°C also shows that the corresponding anion **4a**, apparently for steric reasons, does not undergo an intramolecular cyclization to a quinoline **5** at this temperature. However, raising the temperature of the solution containing **4a** to 23°C induced the cyclization reaction to give the quinoline **5** in a high yield.[13] We have thus shown that lithium dialkylamides can mediate highly efficient and chemoselective transformations of readily available Schiff's bases.

ACKNOWLEDGMENTS are made to the Petroleum Research Fund, administered by the American Chemical Society, and NIH (Grants # AI27196 and SO7-RR07171) for support of this research. The Varian VXR-400 NMR spectrometer was obtained with partial support from an award by the NSF Chemical Instrumentation Program (CHEM-8409599).

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8. *Schiff's bases* **1a-e** *were obtained by heating a mixture of the respective aniline and* ketone in toluene in the presence of *p*-toluenesulfonic acid for 10h with azeotropic removal of water. Analytically pure samples were obtained by crystallization from ether/hexanes: **1a**, mp 74-75°C; **1b**, mp 68-70°C; **1c**, mp 22-25°C; **1d**, mp 82-83°C; **1e**, mp 49-51°C.
9. General procedure: a solution of LDA was prepared by adding n-BuLi (3.0 mmol) in hexanes to diisopropylamine (3.1 mmol) in ethyl ether (10 mL) at -10°C. The solution was then cooled, treated with a Schiff's base (1 mmol) in ethyl ether (5 mL), and the mixture was allowed to react under the following conditions: **1a-c**, -50°C, 1h; **1d**, **e**, -20°C, 3h. The mixture was then quenched with aqueous tetrahydrofuran (1:1, 0.2 mL), dried (Na_2SO_4), filtered, and concentrated.
10. The adducts **2a-c** were purified by chromatography on silica gel (hexanes/NEt_3/EtOH, 7:2:1) at 0°C.

    2a: yield 92%, an oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=7.4 Hz, Me of Et) 1.31 and 1.33 (2d, J=7 Hz, Me of i-Pr), 1.90 (m, 1H, J=14 Hz, J=7.4 Hz, CH_2), 2.01 (m, 1H, J=14 Hz, J=7.4 Hz, CH_2), 3.74 (septet, J=7 Hz, CH of i-Pr), 4.32 (br s, NH), 6.59 (t, J=8 Hz, H5 of PhCN), 6.62 (d, J=8 Hz, H3 of PhCN), 7.09 (t, J=8 Hz, H4 of PhCN), 7.12 (t, J=7.5 Hz, H4 of Ph), 7.20 (d, J=8 Hz, H6 of PhCN), 7.23 (t, J=7.5 Hz, H3 and H5 of Ph), 7.42 (d, J=7.5 Hz, H2 and H6 of Ph); FT-IR (film) ν 2212, 3384 cm^{-1}; MS m/z (%) 306(100), 335(1, M^+). Anal. (C, H, N).

2b: an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 and 0.87 (2d, J=6.4 Hz, Me of i-Bu), 1.28 and 1.34 (2d, J=7 Hz, Me of i-Pr), 1.93 (m, CH and CH_2 of i-Bu), 3.72 (sept, J=7 Hz, CH of i-Pr), 4.40 (br s, NH), 6.57 (t, J=8 Hz, H5 of PhCN), 6.63 (d, J=8 Hz, H3 of PhCN), 7.09 (t, J=8 Hz, H4 of PhCN), 7.12 (t, J=8 Hz, H4 of Ph), 7.18 (d, J=8 Hz, H6 of PhCN), 7.21 (t, J=8 Hz, H3 and H5 of Ph), 7.41 (d, J=8 Hz, H2 and H6 of Ph). Anal. (C, H, N).

2c: an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=7 Hz, Me of Et), 1.33 (d, J=7 Hz, Me of i-Pr), 2.65 (br s, NH), 2.69 (q, J=7 Hz, CH_2 of Et), 3.70 (sept, J=7 Hz, CH of i-Pr), 6.77 (d, J=8 Hz, H3 and H5 of PhCN), 7.25 (d, J=8 Hz, H2 and H6 of PhCN), 7.42-7.52 (m, 5H, Ph); MS (EI; m/z, %) 292(100), 334(22), 335(20, M+); MS (CI with isobutane; m/z, %) 292(45), 336(100, M^+ + 1). HR-MS. Calcd for $C_{22}H_{29}N_3$: m/z 335.2361. Found: m/z 335.2357.

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12. However, neither **3** (R^1=o-CN, R^2=H) nor **3b** could be prepared from the respective Schiff's bases **1** (R^1=o-CN, R^2=H) and **1b**. Quenching of the mixtures with D_2O gave **1** (R^1=o-CN, R^2=D) and **1b**, respectively. Apparently **3** (R^1=o-CN, R^2=D) tautomerizes quickly, and sterically hindered **1b** is not lithiated with the sterically hindered base LTMP. The enamines **3a**, **3c-e** were obtained as mixtures of diastereomers; **3a**, Z/E=3:2, mp 74-84°C; **3c**, Z/E=1:3, an oil; **3d**, Z/E=1:1, an oil; **3e**, Z/E=1:3, an oil. All compounds **3a**, **3c-e** gave IR absorption at ϑ=3360±10 cm^{-1} (N-H). The ^{1}H NMR spectra (400 MHz, $CDCl_3$/TMS) are given below. The assignments are based on proton decoupling and NOE experiments.

(Z)-3a: δ 1.80 (d, J=7 Hz, Me), 5.89 (q, J=7 Hz, vinyl), 5.93 (br s, NH), 6.43 (d, J=8 Hz, H3 of PhCN), 6.71 (t, J=8 Hz, H5 of PhCN), 7.22 (t, J=8 Hz, H4 of PhCN), 7.24-7.45 (m, 6H).

(E)-3a: δ 1.85 (d, J=7 Hz, Me), 5.70 (q, J=7 Hz, vinyl), 6.13 (br s, NH), 6.70 (d, J=8 Hz, H3 of PhCN; t, J=8 Hz, H5 of PhCN), 7.19 (t, J=8 Hz, H4 of PhCN), 7.24-7.47 (m, 6H).

(Z)-3c: δ 1.78 (d, J=7 Hz, Me), 5.60 (br s, NH), 5.83 (q, J=7 Hz, vinyl), 6.57 (d, J-8 Hz, H3 and H5 of PhCN), 7.28-7.42 (m, 7H).

(E)-3c: δ 1.83 (d, J=7 Hz, Me), 5.67 (q, J=7 Hz, vinyl), 5.77 (br s, NH), 6.66 (d, J-8 Hz, H3 and H5 of PhCN), 7.28-7.42 (m, 7H).

(Z)-3d: δ 1.78 (d, J=7 Hz, Me), 5.37 (br s, NH), 5.75 (q, J=7 Hz, vinyl), 6.6-7.5 (m, 9H).

(E)-3d: δ 1.81 (d, J=7 Hz, Me), 5.40 (br s, NH), 5.58 (q, J=7 Hz, vinyl), 6.6-7.5 (m, 9H).

(Z)-3e: δ 1.78 (d, J=7 Hz, Me), 5.30 (br s, NH), 5.59 (q, J=7 Hz, vinyl), 6.4-7.5 (m, 10H).

(E)-3e: δ 1.80 (d, J=7 Hz, Me), 5.20 (br s, NH), 5.42 (q, J=7 Hz, vinyl), 6.4-7.5 (m, 10H).

13. LTMP (2 mmol) in ether was treated with a solution of **1a** (1 mmol) in ether at -10°C, and the resultant mixture (ca 10 mL) was allowed to stand at 23°C for 3 h, and then quenched with H_2O. Chromatography on silica gel (hexanes/Et_3N/EtOH, 7:2:1) gave **5**: yield 77%, mp 137-138°C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 2.24 (s, Me), 4.74 (br s, NH_2), 7.41 (m, H4 of Ph), 7.44-7.49 (m, H3 and H5 of Ph, H6 of Quin), 7.52-7.56 (m, H2 and H6 of Ph), 7.63 (m, H7 of Quin), 7.76 (d, J=8 Hz, H5 of Quin), 8.04 (d, J=8 Hz, H8 of Quin). Anal. (C, H, N).

(Received in USA 2 June 1989)