ISOMERIZATIONS OF SMALL RING LITHIUM DIALKYLAMIDES

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Abstract   Lithium N-butylcyclopropylamide (1) and lithium N-propylcyclobutylamide (2) rearrange in ethereal solvents by nucleophilic eliminative ring fission processes, amide 1 is highly reactive whereas amide 2 is somewhat stable

The application of molecular probes which can undergo skeletal rearrangement upon conversion to a reactive intermediate is becoming increasingly popular for studies of the mechanistic details of reactions of organometallic reagents   Recently, evidence has been presented that electron transfer from hindered lithium dialkylamide bases to appropriate organic substrates can occur [2] We have initiated studies of two classes of metal dialkylamides which potentially could serve as mechanistic probes for electron transfer reactions of hindered dialkylamide bases by implicating the intermediacy of aminyl radicals   The two classes of probes are the strained small ring cycloalkylamides 1 and 2 and pentenylamides [3] The cyclic probes could function as shown in eq 1 and 2, the second steps, the aminyl radical rearrangements, have recently been reported [4] The N-propylcyclobutylaminyl radical opens at a rate comparable to that of the cyclization of the 5-hexenyl radical, a useful mechanistic tool,[5] and the N-butylcyclopropylaminyl radical opens at even a faster rate.[4] Despite the precedence for radical rearrangements, probes like 1 and 2 could be expected to undergo anionic rearrangements to form carbanionic products with the same skeletons as the radical products (vide infra) Herein we report rearrangements of 1 and 2 which define the limits of the utility of these species as mechanistic probes
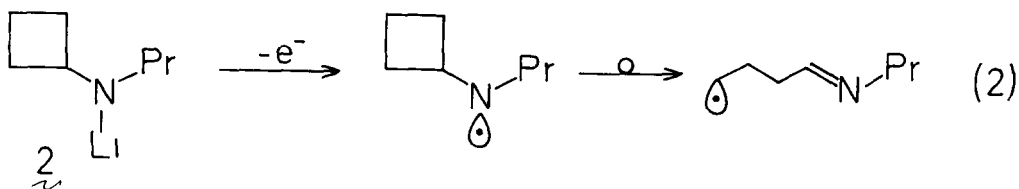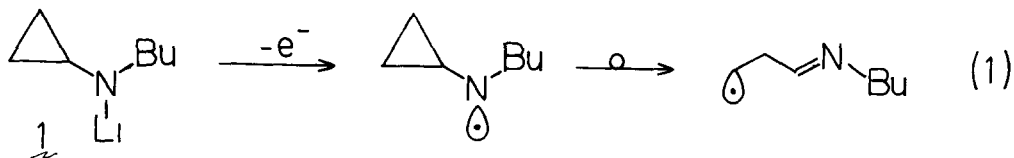
Lithium N-butylcyclopropylamide ($\underset{\sim}{1}$) was produced by treatment of N-butylcyclopropylamine[4] ($\underset{\sim}{3}$) in tetrahydrofuran (THF) with 0 9-1 0 molar equiv of n-butyllithium in hexane at -78 °C or -98 °C or by treatment of the parent amine in ether with 1 0 molar equiv of low halide methyllithium in ether at -98 °C. The solutions were permitted to warm, and the reaction mixtures were quenched by the addition of excess methanol followed by 3% aqueous ammonia solution The yields of amine $\underset{\sim}{3}$ and N-propylidenebutylamine ($\underset{\sim}{4}$)[6] were determined by gc (Table, Runs 1-4)

In a similar manner, lithium N-propylcyclobutylamide ($\underset{\sim}{2}$) was prepared from N-propylcyclo-butylamine[4] ($\underset{\sim}{5}$)   When solutions of amide $\underset{\sim}{2}$ were warmed and the reaction mixtures subsequently were quenched, amide $\underset{\sim}{2}$ was found to be substantially stabler than $\underset{\sim}{1}$ (Table, Runs 5-8) Since $\underset{\sim}{2}$ apparently was relatively stable, we studied the reaction in some detail at 0 °C In kinetic studies involving quenching and gc analysis as described above, amide $\underset{\sim}{2}$ (0 13 N) in THF decomposed with a first order rate constant for disappearance over 1.5 half-lives of $2\ 7 \pm 0\ 6 \times 10^{-4}$ sec^{-1} (average of six runs, the error limit is one standard deviation of the slopes). Despite the reproducibility of these measurements, the reaction clearly is complicated Extrapolation of the first order kinetic log plots to time zero reproducibly gave an intercept at ca 75% yield of amine showing that a rapid reaction consumed ca. 25% of the amide   Further, imine product $\underset{\sim}{6}$[6] was never found in greater than 40% yield in these kinetic studies   Finally, after 1 5 half-lives, the rate of loss of cyclic amine $\underset{\sim}{5}$ rapidly dropped off   We observed little effect on the rate of decomposition of $\underset{\sim}{2}$ when the solvent was changed to ether or when the reaction was run in THF with 2.0 molar equiv of hexamethylphosphoramide added, for these reactions of 0 13 N $\underset{\sim}{2}$ at 0 °C, amide $\underset{\sim}{2}$ decomposed with rate constants of $2\ 4 \times 10^{-4}$ sec^{-1} and $3\ 5 \times 10^{-4}$ sec^{-1}, respectively (average of two runs each)

Table   The stability of lithium amides $\underset{\sim}{1}$ and $\underset{\sim}{2}$

Run #	Amide	concn (N)	solvent	temp (°C)[a]	time (h)	% yield[b] amine[c]	imine[d]
1	$\underset{\sim}{1}$	0 085	ether	-98	0 75	88	0
2[e]	$\underset{\sim}{1}$	0 12	THF	-78	0 5	9	30-48
3	$\underset{\sim}{1}$	0.085	ether	-32	0 5	0	66
4	$\underset{\sim}{1}$	0 085	ether	0	0 5	0	50
5	$\underset{\sim}{2}$	0 085	THF	-98	1 5	92	0
6[e]	$\underset{\sim}{2}$	0 12	THF	-78	0 5	95-100	0
7	$\underset{\sim}{2}$	0 10	ether	-15	2 0	100	0
8	$\underset{\sim}{2}$	0 082	ether	25	24	12	48

[a] Amide solutions were prepared at -98 of -78 °C (0 5 h) and warmed to the desired temperatures. After the desired reaction period, the solutions were cooled to -78 °C and quenched
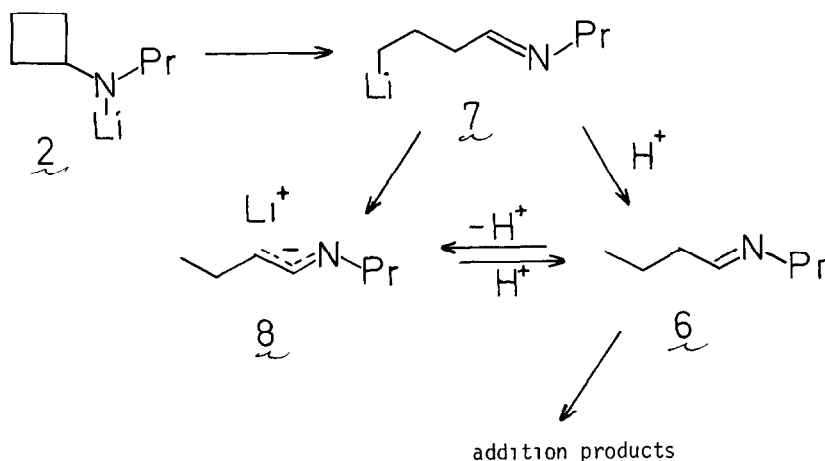
[b] Percent yields determined by gc, an internal standard of n-decane was used

[c] For amides $\underset{\sim}{1}$ and $\underset{\sim}{2}$, the parent amines are $\underset{\sim}{3}$ and $\underset{\sim}{5}$, respectively

[d] For amides $\underset{\sim}{1}$ and $\underset{\sim}{2}$, the imine products are $\underset{\sim}{4}$ and $\underset{\sim}{6}$, respectively

[e] Range of two determinations.

SCHEME

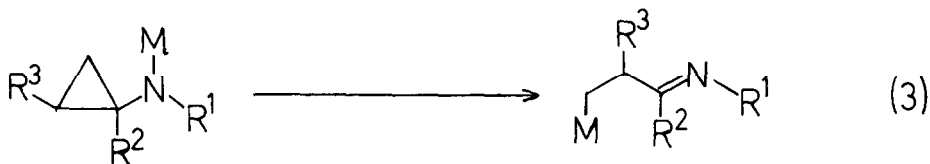Lithium amides $\underset{\sim}{1}$ and $\underset{\sim}{2}$ presumably decompose by an initial thermal rearrangement, a nucleophilic eliminative ring fission, as shown in the Scheme for amide $\underset{\sim}{2}$. Isomerization of $\underset{\sim}{2}$ to the lithium reagent $\underset{\sim}{7}$ would be followed by a rapid isomerization (or intermolecular reaction) of $\underset{\sim}{7}$ to give azaallyllithium reagent $\underset{\sim}{8}$. Any $\underset{\sim}{7}$ which reacted with an acidic source would give imine $\underset{\sim}{6}$ which could then be deprotonated by $\underset{\sim}{2}$ or $\underset{\sim}{7}$ to give $\underset{\sim}{8}$ Such a sequence, with $\underset{\sim}{2}$ deprotonating $\underset{\sim}{6}$, could explain why the rate of decomposition of $\underset{\sim}{2}$ slowed dramatically after ca 1 5 half-lives However, at least one other reaction of imine $\underset{\sim}{6}$ must occur leading to the low yield of $\underset{\sim}{6}$ [6] The simple mechanistic picture of the Scheme does not account for the rapid disappearance of the first 25% of amide $\underset{\sim}{2}$, a phenomenum for which we have no good rationalization [7]

The mechanism of the Scheme has precedent in numerous cyclopropylcarbinyl anion ring openings, in cyclobutylcarbinyl anion ring openings, and in openings of cyclopropyl and cyclobutyl alkoxides.[8,9] Nucleophilic eliminative ring fissions of cyclopropyl- and cyclobutylamines containing electron withdrawing groups on the ring under basic or neutral conditions have been reported[8] as have the openings of the unactivated cyclopropylamide systems in eq 3 The bromomagnesium amide $\underset{\sim}{9c}$ was stable at -60 $^\circ$C and cleaved at 20 $^\circ$C [12] We are not aware of examples of cleavages of unactivated cyclobutylamides, in fact, a cyclobutylamide aluminate intermediate related to $\underset{\sim}{9a}$ and $\underset{\sim}{9b}$ did not cleave [10]

Despite the precedence for the pathway outlined in the Scheme, there is a caveat Probes $\underset{\sim}{1}$ and $\underset{\sim}{2}$ were conceived based upon the facile openings of their corresponding aminyl radicals,[4] and we cannot exclude the possibility that radical pathways for the openings occur. Such a process might involve oxidation followed by aminyl ring opening and electron transfer in a radical chain reaction Nevertheless, our results define the utility of lithium amides $\underset{\sim}{1}$ and $\underset{\sim}{2}$ as mechanistic probes, the cyclopropylamide $\underset{\sim}{1}$ is too reactive to be useful, but lithium N-propylcyclobutylamide ($\underset{\sim}{2}$) is stable enough to permit its application as a probe

$$R^3 \triangle \underset{R^2}{\overset{\overset{M}{|}}{\underset{}{N}}} R^1 \longrightarrow \underset{M}{\overset{R^3}{\underset{}{}}} \overset{}{\underset{R^2}{C}} = N - R^1 \qquad (3)$$

9a $\quad$ M = AlR_3^-, R^1 = Ph or CH_2CH_2Ph, R^2 = R^3 = H (ref 10)

9b $\quad$ M = AlR_3^-, R^1 = CH(i-Pr)$_2$, R^2 = H, R^3 = t-Bu (ref 11)

9c $\quad$ M = MgBr, R^1 = R^3 = H, R^2 = Ph (ref 12)

References and Notes

1) Camille and Henry Dreyfus Teacher-Scholar, 1980-1985

2) L T Scott, K J Carlin, and T H. Schultz, Tetrahedron Lett., 4637 (1978), X Creary, J Org. Chem , 45, 2419 (1980), M Newcomb and R A. Reeder, ibid., 45, 1489 (1980), E C Ashby, A B Goel, and R N DePriest, ibid , 46, 2429 (1981), G R Newkome and D C Hager, ibid , 47, 599 (1982)

3) Studies of the thermal isomerizations of a representative lithium pentenylamide are discussed in the accompanying communication

4) Y Maeda and K U Ingold, J Am Chem Soc , 102, 328 (1980)

5) A L J Beckwith and K U Ingold in "Rearrangements in Ground and Excited States", P de Mayo, Ed., Academic Press, London, 1980, Essay 4

6) Imines 4 and 6 from the decomposition of 1 and 2, respectively, were identical to authentic samples by gc retention times on SE-30 and Pennwalt 223   In a control reaction, imine 6 was treated with 1 2 molar equiv of lithium diisopropylamide at -78 ^{o}C and the resulting mixture was warmed to 0 ^{o}C for 13 min and then the reaction mixture was quenched, we obtained only a 50-57% return of imine 6

7) In the HMPA reactions run in THF, we again observed a rapid loss of ca 25% of 2   In the kinetic reactions run in ether only ca. 10% of 2 was lost rapidly

8) C J. M Stirling, Chem Rev , 78, 517 (1978)

9) E A. Hill, J Organometal Chem , 91, 123 (1975)

10) C L Bumgardner, E L Lawton, and J G Carver, J. Org Chem , 37, 407 (1972)

11) H Quast and R Frank, Liebigs Ann. Chem , 1980, 1939 (1980)

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