METAL-HALOGEN EXCHANGE-INITIATED CYCLIZATION
OF IODO CARBONYL COMPOUNDS

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SUMMARY: The feasability of constructing carbocycles through the metal-halogen exchange-initiated cyclization reactions of iodoketones and other carboxyl derivatives has been studied. With saturated primary iodides, cyclization predominates when deactivated ketones are employed.

Lithium-halogen exchange has become an important method for the generation of nucleophilic centers. Exchange reactions used to initiate intramolecular reactions have usually involved aryl[1] or vinyl halides.[2] We have recently observed that the rates of lithium-iodine exchange reactions of primary saturated iodides in some cases are rapid enough to permit the formation of unstabilized nucleophilic centers in the presence of electrophilic groups such as α,β-unsaturated esters with which they may subsequently undergo intramolecular Michael addition reactions.[3,4] We have now explored the possibility of likewise initiating other cyclization reactions using model compounds containing commonly occurring carbonyl groups.
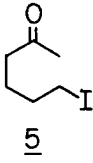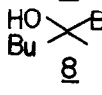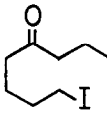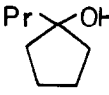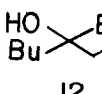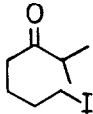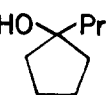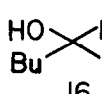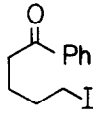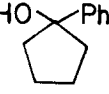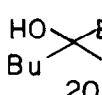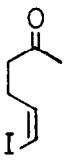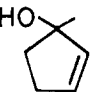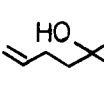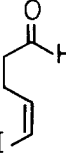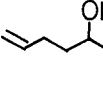
While the cyclization reactions of haloketones through the use of reductive[5] and related Barbier-type[6] conditions have been well studied[7], we are unaware of attempts to initiate cycloalkanol formation by lithium-halogen exchange reactions as shown in Scheme 1. Success requires that metal-halogen

SCHEME 1

$$\underline{4} \quad (X = I, H)$$
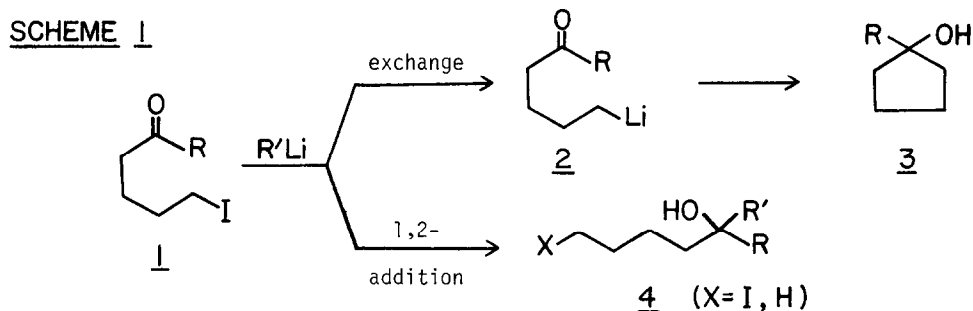
exchange and subsequent cyclization ($1{\to}2{\to}3$) be faster than attack of the carbonyl group by the metalating agent, RLi ($1{\to}4$). The structural requirements for meeting these conditions have been examined and the results of studies with model compounds are shown in Table 1. Only 5-membered ring formation has been examined to date.

Treatment of methyl ketone **5** with n-BuLi at -100°C gives rise to comparable amounts of cyclization product **6** (21%) and 1,2-carbonyl adduct **7** (35%) in addition to a sizable amount of starting material (**5**) arising from enolization.[8] The use of excess t-BuLi[9] results in a slight improvement in the

Table 1. Reaction of Iodo Carbonyl Compounds[12] with Alkyllithium Reagents [a,b].

Compound	RLi (equiv.) solv. T(°C)	Products[c] (yield,%)[d]		
5	n-BuLi (1.25) THF −100	**6** (21)	**7** (35)	**5** (34)[e]
	t-BuLi (4) Et$_2$O −78	**6** (26)	**8** (21)	**9** (23)
10	t-BuLi (4) Et$_2$O −78	**11** (49)	**12** (47)	**13** (4)
	Et$_2$O 0	**11** (25)	**12** (23)	**13** (trace)
14	t-BuLi (4) Et$_2$O −78	**15** (78)	**16** (16)	**17** (8)
	t-BuLi (2.2) BF$_3$·Et$_2$O (1.0) Et$_2$O −78	**15** (82)	**16** (18)	
	n-BuLi (1.2) Et$_2$O −78	**15** (0)	**14** (66)[e]	
18	t-BuLi (2.2) THF −78	**19** (66)[f]	**20** (6)	**21** (7)
	(4) THF 0	**19** (25)[f]	**20** (12)[f]	**21** (20)[f]
22	t-BuLi (2.2) Et$_2$O −78	**23** (20)	**24**, R=[t]Bu (20)	
	n-BuLi (1.4) THF −78	**23** (87)	**24**, R=[n]Bu (1)	
25	t-BuLi (4) Et$_2$O −78	**26** (4)	**27**, R=[t]Bu (20)	
	n-BuLi (3) THF −78	**26** (40)	**28**, R=[n]Bu (36)	

[a] New iodides gave satisfactory analyses. [b] Ketones were treated over 30 sec. with RLi and quenched with water after 10 min. [c] Products were identified by comparison with authentic samples. [d] Determined by g.c. [e] Product absent by g.c. when reaction quenched with Me$_3$SiCl. [f] Isolated yield.
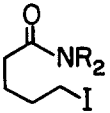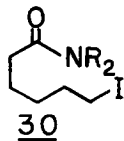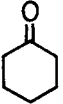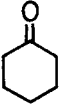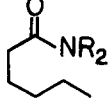
relative amount of cyclization product (6). Under similar conditions propyl ketone **10** also gives approximately equal amounts of cyclized product (**11**) and carbonyl addition product (**12**) (devoid of iodine as a result of excess _t_-BuLi)[9] but unlike the case of methyl ketone **5**, enolization (leading to **13**) is minor (4%). Branched iodoketone **14** gives a sizable increase in the proportion of cyclic alcohol **15** when treated with _t_-BuLi.

Treatment of phenyl ketone **18** with _t_-BuLi at -78°C also results in satisfactory exchange-induced cyclization giving **19** in 66% isolated yield. This result is notable since there is some evidence suggesting that conjugation increases the rate at which carbonyl groups react with alkyllithium reagents.[10] A marked deteriation is observed when the reaction is conducted at 0°C, however, with increased production of products resulting from carbonyl addition (**20**) and enolization (**21**).

The reaction of vinyl iodide **22** with _t_-BuLi gives equal amounts of cyclization product **23** and carbonyl addition product **24** while the use of _n_-BuLi results in nearly exclusive formation of cyclic **23** (87%). The favorable cyclization to carbonyl addition ratio in the latter case is likely the result of an increased rate of metal-halogen exchange of the vinyl iodide relative to the saturated iodide in **5** wherefore the similarity of the mixture obtained in the former case (**23:24** = 1:1) with that from saturated analog **5** (**6:7** = 1.2:1) suggests that the rate of ring closure of the intermediate vinyllithium from **22** is slower than its saturated analog.

Equally instructive is the case of aldehyde **25** where treatment with _t_-BuLi gives predominantly 1,2-addition product **27** while the use of _n_-BuLi results in the formation of approximately equal amounts of cyclization product **26** and **28**. It is noteworthy that the increased rate of vinyl iodide exchange allows exchange-initiated cyclization to be competitive with _n_-BuLi addition to an aldehyde group.

Table 2. Reaction of Iodoamides with Alkyllithium Reagents[a]

Amide	R	RLi	Product (yield, %)[b]		
29 (iodoamide)	_i_-Pr	_n_-BuLi	cyclopentanone (71)[c,d]		
30 (iodoamide)	Et	_n_-BuLi	cyclohexanone (15)	amide NR₂ (5)	
	_i_-Pr	_n_-BuLi	(0)	(<5)[d]	
	_i_-Pr	_t_-BuLi	(0)	(88)	

[a] Reactions conducted at -78°C by the addition over 30 sec of 1.2 equiv. of _n_-BuLi or 2.2 equiv. of _t_-BuLi to iodides in THF or Et₂O, respectively, followed by quenching with dil. HCl after 1-4 hr. [b] Determined by g.c. [c] Based on _n_-BuI formed. [d] Side-products not identified.

We have also examined several model iodoamides as substrates for exchange initiated cyclization reactions and results are shown in Table 2. Treatment of unstable diisopropylamide **29** in THF with _n_-BuLi at 78°C followed by quenching (aq. HCl), also at -78°C, results in the formation of cyclopentanone in 71% yield (based on exchange-produced _n_-BuI). The great sensitivity of δ-iodoamides to intramolecular alkylation will likely limit the utility of this reaction, however. Much poorer results are seen in more stable homologs **30**. Treatment of **30** (R=Et) with _n_-BuLi results in an only 15% yield of cyclohexanone while no cyclic ketone could be obtained from the corresponding diisopropylamides (**30**,

R=*i*-Pr).

(Eq. 1)
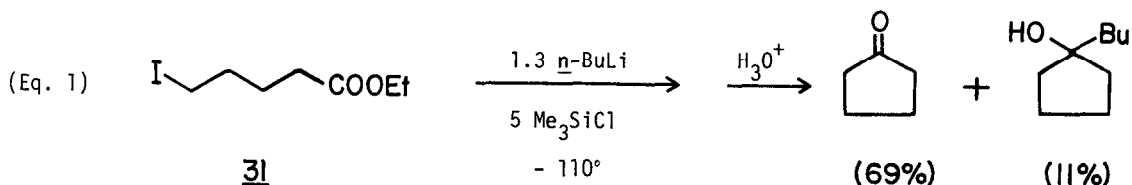
Finally, we have examined a model ester, ethyl 5-iodovalerate (**31**), shown in eq. 1. Treatment of **31** with *n*-BuLi at -110°C in the presence of excess Me₃SiCl (added to trap the intermediate tetrahedral carbonyl adduct, thereby preventing tertiary alcohol formation which would result from premature ketone formation)[11] gives, after hydrolysis of the intermediate silyoxyketal, cyclopentanone (69%) along with a small amount of 1-butylcyclopentanol (11%) resulting from incomplete interception of the carbonyl adduct.

We are currently examining the scope of these and other promising exchange-initiated cyclization reactions.

References and Notes

1. (a) W. E. Parham, L. E. Jones and Y. Sayed, *J. Org. Chem.* 1978, **40**, 2394; (b) R. J. Boatman, B. J. Whitlock and H. W. Whitlock, Jr., *J. Am. Chem. Soc.* 1977, **99**, 4822.

2. (a) E. Negishi and J. A. Miller, *ibid.* 1983, **105**, 6761; (b) L. D. Boardman, V. Bagheri, H. Sawada and E. Negishi, *ibid.* 1984, **106**, 6105.

3. M. P. Cooke, Jr., *J. Org. Chem.* 1984, **49**, 1144.

4. Exchange-initiated intramolecular alkylation reactions of saturated iodides have recently been reported: W. F. Bailey and R. P. Gagnier and J. J. Patricia, *ibid.* 1984, **49**, 2098.

5. G. A. Molander and J. B. Etter, *Tetrahedron Lett.* 1984, **25**, 3281. Also see E. J. Corey and I. J. Kuwajima, *J. Am. Chem. Soc.* 1970, **92**, 395.

6. C. Blombert and F. A. Hartog, *Synthesis* 1977, 18.

7. For a good review of this area see ref. 1 in ref. 5.

8. This product is absent upon g.c. analysis if the reaction mixture is quenched with Me₃SiCl.

9. E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.* 1972, **94**, 7210.

10. D. Seyserth, R. M. Simon, D. J. Sepelak and H. A. Klein, *ibid.* 1983, **105**, 4634.

11. Predominantly alcohol formation is observed in the absence of Me₃SiCl. The scope and utility of this technique for the direct acylation of organolithium reagents will be reported shortly.

12. Iodides **5**, **10**, **14** and **18** were prepared by addition of the appropriate Grignard reagent to 5-chloro-pentanal, oxidation (CrO₃Cl·HPy) and halide exchange (NaI-acetone). Aldehyde **25** was prepared by copper catalyzed Normant addition of 3,3-dimethoxypropylmagnesium bromide to acetylene (Me₂S-CuBr), iodination (I₂) and hydrolysis (50% HOAc). Grignard addition (MeMgBr) to **25** and Jones oxidation gave **22**.