Reaction of Organolithium Reagents with Lactim Ethers: Preparation of Cyclic 2-Alkyl Imines or 2,2-Dialkyl Amines[1a]

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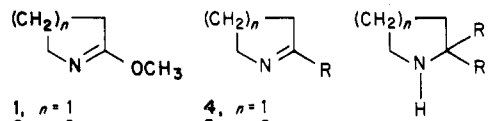
The reaction of lactim ethers **1–3** with organolithium reagents has been found to be an effective method for the preparation of cyclic 2-alkyl imines **4–6**. The method is most effective for the preparation of 2-aryl and sterically hindered 2-alkyl imines. In addition, treatment of **1–3** with excess organolithium provides a facile route to the rare cyclic 2,2-dialkyl amine derivatives **7–9**. These reactions are characterized by mild reaction conditions and good yields and constitute a superior route to the title compounds.

Our interest in cyclic 2-alkyl imines as synthons for indolizidine and quinolizidine alkaloids[2] led to a search for synthetic approaches to these compounds. Methods are available for the preparation of **4** in good yield but these



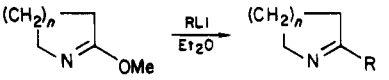
1, $n = 1$; **2**, $n = 2$; **3**, $n = 3$ — **4**, $n = 1$; **5**, $n = 2$; **6**, $n = 3$ — **7**, $n = 1$; **8**, $n = 2$; **9**, $n = 3$

a, R = Me; **b**, R = *n*-Pr; **c**, R = *n*-Bu; **d**, R = *i*-Bu; **e**, R = Ph

did not give **5** or **6** in useful amounts. The method used most often was the addition/elimination sequence observed upon reaction of lactim ethers (cyclic imidates) **1–3** and Grignard reagents. This reaction has produced 60–85% of **4** from **1**[3] but similar reaction with **2** or **3** gave **5** or **6** in only 0–50% yield[4] and is generally unsatisfactory. When highly reactive Grignard reagents such as allylmagnesium iodide reacted with **1**, the dialkyl amine **7** (R = alkyl) was the only product reported,[5,6] presumably via reaction of the initially formed imine with the Grignard reagent. Acyclic imidates also react with Grignard reagents to give mixtures of 2-alkyl imines and 2,2-dialkyl amines.[7] Similarly, 4-chlorobutanenitrile, upon treatment with Grignard reagents, has been shown to give **4** in good yield.[8] Seeman has also reported that *N*-vinylpyrrolidinone, upon treatment with an organolithium reagent and then strong aqueous acid, gave **4** in moderate yield.[5] Each of the methods previously reported were characterized by low yields or harsh reaction and/or workup conditions.

We have examined the reaction of **1–3** with organolithium reagents in an attempt to obtain the desired 2-alkyl imines under more moderate reaction conditions and in higher yields. Previous work had shown that acyclic imidates react with organolithium reagents to give imines but, as with Grignard reagents, dialkyl amines are produced in significant amounts, apparently via carbene intermediates.[9] LaLonde has noted that reaction of phenyllithium

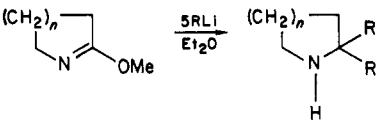
Table I. Reaction of Lactim Ethers 1–3 with 1 Equiv of Organolithium Reagents To Give Cyclic 2-Alkyl Imines 4–6



imidate	R[a]	4[c], %	imine[e]	yield,[c] %	amine[e]	yield,[c] %
1	Me	95	**4a**[3]	4	**7a**	
	n-Pr	52	**4b**[5]	11	**7b**[d]	35
	n-Bu	38	**4c**[3]	34	**7c**[4,4a]	24
	t-Bu	51	**4d**[21]	49	**7d**	
	Ph[b]	5	**4e**[3]	85	**7e**[20]	
2	Me	100	**5a**		**8a**	
	n-Pr	43	**5b**[22]	13	**8b**[23]	25
	n-Bu	43	**5c**[4a]	21	**8c**[d]	25
	t-Bu		**5d**[d,3,22]	19	**8d**	
	Ph[b]	53	**5e**[20]	47	**8e**	
3	Me	86	**6a**[6]	8	**9a**	
	n-Pr	45	**6b**[5b,6]	21	**9b**[d]	27
	n-Bu	57	**6c**[6]	9	**9c**[d]	33
	t-Bu	66	**6d**[d]	34	**9d**	
	Ph[b]	13	**6e**[6]	67	**9e**	

[a] −24 °C. [b] 25 °C. [c] Yield via VPC with pyridine as an internal standard.[19] [d] Satisfactory analysis obtained for this compound. [e] Full spectral data available as supplementary material.

Table II. Reaction of Lactim Ethers 1–3 with 5 Equiv of Organolithium Reagents To Give Cyclic 2,2-Dialkyl Amines 7–9



imidate	R[a]	4,[c] %	imine[e]	yield,[c] %	amine[e]	yield,[c] %
1	*n*-Pr		**4b**		**7b**[d]	67
	n-Bu		**4c**		**7c**[d,4a]	75
	t-Bu		**4d**[21]	13	**7d**[d]	49
	Ph[b]		**4e**		**7e**[d,20]	74
2	*n*-Pr	6	**5b**		**8b**[23]	63
	n-Bu	9	**5c**		**8c**[d]	65
	t-Bu		**5d**[d,3,22]	68	**8d**	
	Ph[b]		**5e**		**8e**[d]	60
3	*n*-Pr		**6b**		**9b**[d]	67
	n-Bu		**6c**		**3c**[d]	68
	t-Bu		**6d**[d]	24	**9d**	
	Ph[b]		**6e**		**9e**[d]	68

[a] −24 °C. [b] 25 °C. [c] Yield via VPC with pyridine as an internal standard.[19] [d] Satisfactory analysis obtained for this compound. [e] Full spectral data available as supplementary material.

(1) (a) Presented, in part, at the 13th Northeast Regional Meeting of the American Chemical Society, *ORGN* 181, Hartford, CT, June 29, 1983. (b) Abstracted, in part, from the M.S. Thesis of C.A.Z.

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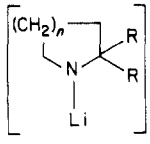
with **2**, at −78 °C, gave **5e** in 50% yield but **5e** was observed *only* upon addition of diisobutylaluminum hydride to the reaction mixture and arises via reaction of phenyllithium with the resultant "ate" complex.[10] Pinnick has shown that **1** did not undergo reaction with 1-lithio-1-cyclopropanecarboxylic acid, ethyl ester although this was attributed to the propensity of the latter reagent for self-condensation.[11] As shown in Table I, we found that **1–3** react with organolithium reagents, in ether at −24 °C, to give moderate yields of **4–6** with reactive organolithium reagents such as *n*-butyllithium, although significant amounts of dialkyl amines **7**, **8**, or **9** were also observed. With less reactive reagents such as phenyllithium, good yields of **4–6** were obtained and without formation of **7–9**. We also found that **1–3**, upon reaction with excess organolithium reagent, gave the 2,2-dialkyl amines **7**, **8**, or **9** in good yield, as shown in Table II.

The requisite lactim ethers **1–3** were prepared from the corresponding lactams by reaction with dimethyl sulfate.[3a] Subsequent treatment of **1** with phenyllithium at 25 °C, in ether, gave 85% **4e**, no **7e**, and 5% recovered **1**. Reaction of **1** with *n*-butyllithium at −24 °C, however, gave 34% **4c**, 24% **7c**, and 38% recovered **1**. In subsequent reactions, the more reactive organolithium reagents gave significant amounts of the 2,2-dialkyl amines **7–9**, in contrast with the less reactive organolithium reagents which gave **4–6**, exclusively. Since **7–9** arise via addition of the organolithium reagent to **4–6**, the recovery of unreacted **1–3** was not surprising when only 1 equiv of organolithium was employed. We also found, however, that deprotonation of **1–3** occurs as a minor process, either by the organolithium or the 2,2-dialkyl amide **10** (formed in situ),



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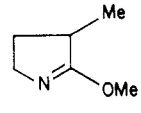

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and accounts for a portion of the recovered **1–3**. This conclusion resulted from the reaction of **1** with *n*-butyllithium which, when quenched with methyl iodide, gave 5-methoxy-4-methyl-3,4-dihydro-2*H*-pyrrole (**11**) in 15% yield. The less basic organolithium reagents gave less deprotonation. Methyllithium proved to be unreactive under a variety of reaction conditions. With the highly reactive *tert*-butyllithium, we isolated only **4d**, without the di-*tert*-butylamine **7d**. It appears that the increased steric demands of **4d** hindered addition of a second equivalent of the bulky reagent.

Reaction of organolithium reagents with **2** and **3**, as shown in Table I, gave results similar to those described for **1**, but only phenyllithium gave good yields of the desired **5e** and **6e**. Although the yields of imine from **2** and **3** were somewhat lower than from **1**, they were better than those reported for similar reaction of **2** and **3** with Grignard reagents.[4] In general, this appears to be an improved method for the preparation of **4–6**, but the requisite separation of **4–6** from **7–9** suggests that only the reactions with aryllithium reagents or hindered organolithium reagents are synthetically useful.

The propensity of **4**, **5**, or **6** to give **7**, **8**, and **9** suggested that reaction of **1–3** with excess organolithium reagent might give the latter amine, directly. Indeed, reaction of **1–3** with 5 equiv of organolithium reagent gave **7–9** in good yield, as shown in Table II, and this appears to be a general and superior route to these amines. It is interesting to note that reaction with excess *tert*-butyllithium gave the 2-alkyl imines **5d** or **6d** in 68% and 24% yields, respectively, rather than **8d** or **9d**. Upon reaction with **1**, however, the pyrroline derivative **4d** was produced in only 13% yield and the 2,2-di-*tert*-butylpyrrolidine **7d** was produced in 49% yield.

The differences in product distribution upon reaction with 1 equiv of organolithium reagent can be accounted for by the nucleophilicity of the organolithium and the steric demands of the organolithium and lactim ether. *n*-Butyllithium has been shown to be more nucleophilic than phenyllithium in addition reactions with carbonyl derivatives[12] and more basic in the deprotonation of ethers[13] whereas methyllithium was much less reactive in both cases. The increased reactivity of *n*-butyllithium when compared to phenyllithium and methyllithium is consistent with this increased nucleophilicity. The steric interactions of the reagent and imidate, however, may not be overlooked. Huet has noted that *n*-butyllithium adds faster than phenyllithium to acyclic ketimines and aldimines to give the corresponding dialkyl amine.[14] He explains this in terms of the greater steric demand of the former reagent upon interaction with the azomethine carbon. A similar argument can be made for reactions of **1–3**.

The facility for conversion of **4–6** to **7–9** is clearly a function of the steric interactions of the alkyl/aryl side chain of the imine and the alkyl/aryl group of the incoming organolithium, as well as the nucleophilicity of the organolithium, as described above. The failure of the highly reactive *tert*-butyllithium to produce dialkyl amines **8d** and **9d** from **2** and **3** is an indication of the powerful effect of the bulky *tert*-butyl group in **5d** and **6d** to inhibit further reaction. The facile formation of **4d**, however, suggests that **1** is less sterically demanding than **2** or **3**.

The small amount of **1–3** which arises via deprotonation can be accounted for by the basicity of the 2,2-dialkyl amide **10** or of the organolithium reagents via kinetic deprotonation. As noted above, the presence of this deprotonation pathway was demonstrated by the isolation of **9** from the reaction of *n*-butyllithium and **1**. Such a reaction is common and similar deprotonation was observed by Trost[15] upon reaction of **2** with lithium dialkylamide at −78 °C. Similar deprotonation of simple imines is also well-known,[16] although we did not observe this process.

In conclusion, we have described a mild method for the formation of cyclic 2-alkyl imines in moderate to good yield which is most useful for 2-aryl imines or 2-alkyl imines when the alkyl group provides significant steric encumbrance. The yields of **4–6** derived from *n*-butyllithium and *n*-propyllithium were reduced due to formation of the 2,2-dialkyl amines, but these were separable via chromatographic techniques. This route provides yields of **5** and **6** which are generally superior to that provided by other methods. The cyclic 2,2-dialkyl amines were subsequently

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produced in good yield, and free of the corresponding imine, simply by treating the appropriate lactim ether with an excess of the organolithium reagent. This method therefore constitutes the superior route to these heretofore rare amines.

Experimental Section

The ^1H NMR spectra were recorded on a Varian Associates Model EM-360-A spectrometer at 60 MHz or a Bruker Model WH-90 spectrometer at 90 MHz. The chemical shifts are reported in ppm, downfield from tetramethylsilane. Mass spectral analyses were obtained on an AEI-MS-902 mass spectrometer. The VPC/MS analyses were obtained on a Hewlett-Packard 5985 VPC/MS system. The reaction mixtures were analyzed via VPC on a 20 ft × $^1/_8$ in., 20% SE-30/Anakron-A column utilizing a Varian Associates Model 3920B gas chromatograph. The elemental analyses were performed by MicAnal of Tucson, AZ.

All glassware was oven-dried and flushed with argon prior to use. The diethyl ether and THF were distilled from $LiAlH_4$ prior to use. All lactim ethers were distilled from anhydrous K_2CO_3 and stored under desiccation. All organolithium reagents were standardized in THF, prior to use, with diphenylacetic acid.[17] The 5-methoxy-3,4-dihydro-2*H*-pyrrole, (**1**), 2-methoxy-3,4,5,6-tetrahydropyridine (**2**), and, 7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine (**3**), were prepared via reaction of the corresponding lactam and dimethyl sulfate.[3] The *n*-propyllithium was prepared in ether (0.79 M) from lithium wire and 1-bromopropane by utilizing the method of Evans.[18] The *n*-butyllithium (1.2 M in hexane), methyllithium (1.33 M in ether), *tert*-butyllithium (1.36 M in pentane), and phenyllithium (1.74 M in cyclohexane/ether) were obtained from Alfa. Anhydrous ether was obtained from Mallinckrodt. Diphenylacetic acid, THF, dimethyl sulfate, $LiAlH_4$, 2-pyrrolidinone, 3,4,5,6-tetrahydro-1*H*-pyridin-2-one, and hexahydroazepin-2-one were obtained from Aldrich.

General Procedure for Preparation of Imines 4–6 or 2,2-Dialkyl Amines 7–9 from Lactim Ethers 1–3. An ether solution of the appropriate lactim ether **1–3** in 25 mL of anhydrous ether, cooled to −24 °C (at 25 °C for phenyllithium), was treated with either 1 or 5 equiv of the organolithium reagent, dropwise, over a period of 10 min. The solution was stirred at −24 °C (at 25 °C for phenyllithium) for 12 h, water was added to quench the reaction, the solution was dried (Na_2SO_4), and the solvents were evaporated at reduced pressure to give the products. Samples for NMR and elemental analyses were obtained via preparative VPC. The crude oil was analyzed by VPC for product distribution by using pyridine as an internal standard.[19]

5-*n*-Butyl-3,4-dihydro-2*H*-pyrrole (4c) and 2,2-Di-*n*-butylpyrrolidine (7c). Reaction of 1.826 g (18.40 mmol) of **1** with 15.3 mL of *n*-butyllithium gave an oil containing 0.783 g (6.26 mmol, 34%) of **4c**[3] [^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.21–1.54 (m, 6 H), 1.68–1.93 (m, 2 H), 2.20 (t, 2 H), 3.61 (t, 2 H); mass spectrum, *m/z* (relative intensity) 125 (2, $M^{+\cdot}$), 110 (100), 82 (22), 57 (24), 41 (15)] 0.809 g (4.42 mmol, 24%) of **7c** [^1H NMR ($CDCl_3$) δ 0.91 (t, 6 H), 1.26–1.34 (m, 12 H), 1.56 (t, 2 H), 1.63–1.73 (m, 2 H), 1.81 (s, 1 H), 2.91 (t, 2 H); mass spectrum, *m/z* (relative intensity) 183 (0.1, $M^{+\cdot}$), 127 (14), 126 (100), 96 (6), 82 (4); calcd for $C_{12}H_{25}N$ 183.1983, found 183.2057].

In addition, 0.694 g (6.99 mmol, 38%) of **1** was recovered.

2-Phenyl-3,4,5,6-tetrahydropyridine (5e). Reaction of 0.417 g (3.69 mmol) of **2** and 2.12 mL of phenyllithium gave an oil containing 0.275 g (1.73 mmol, 47%) of **5e**:[20] ^1H NMR ($CDCl_3$) δ 1.60–1.97 (m, 4 H), 2.62 (t, 2 H), 3.63 (t, 2 H), 6.91–7.24 (m, 3 H), 7.44–7.71 (m, 2 H); mass spectrum, *m/z* (relative intensity) 159 (77, $M^{+\cdot}$), 158 (94), 104 (51), 103 (100).

In addition, 0.222 g (1.96 mmol, 53%) of **2** was recovered.

2,2-Di-*n*-butylpyrrolidine (7c). Reaction of 0.327 g (3.30 mmol) of **1** and 7.60 mL of *n*-butyllithium gave an oil containing 0.454 g (2.48 mmol, 75%) of **7c**.[4a]

2,2-Diphenylpiperidine (8e). Reaction of 0.399 g (3.52 mmol) of **2** and 10.1 mL of phenyllithium gave an oil containing 0.500 g (2.11 mmol, 60%) of **8e**: ^1H NMR ($CDCl_3$) δ 1.39–1.81 (m, 4 H), 1.91 (s, 1 H), 2.45 (t, 2 H), 2.80 (t, 2 H), 7.15–7.89 (m, 10 H); mass spectrum, *m/z* (relative intensity) 237 (49, $M^{+\cdot}$), 236 (48), 208 (94), 194 (53), 160 (100); calcd for $C_{17}H_{19}N$ 237.1519; found 237.1517.

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Registry No. **1**, 5264-35-7; **2**, 5693-62-9; **3**, 2525-16-8; **4a**, 872-32-2; **4b**, 872-81-1; **4c**, 64319-86-4; **4d**, 51269-70-6; **4e**, 700-91-4; **5a**, 1462-92-6; **5b**, 1604-01-9; **5c**, 1462-94-8; **5d**, 90949-17-0; **5e**, 57050-07-4; **6a**, 3338-03-2; **6b**, 3338-05-4; **6c**, 3338-06-5; **6d**, 92144-55-3; **6e**, 3338-00-9; **7b**, 92144-56-4; **7c**, 74856-36-3; **7d**, 92144-57-5; **7e**, 68007-29-4; **8b**, 91249-14-8; **8c**, 92144-58-6; **8d**, 92144-59-7; **8e**, 92144-60-0; **9b**, 3311-49-7; **9c**, 3311-50-0; **9d**, 92144-61-1; **9e**, 92144-62-2; **11**, 92144-63-3; MeLi, 917-54-4; PrLi, 2417-93-8; BuLi, 109-72-8; *t*-BuLi, 594-19-4; PhLi, 591-51-5.

Supplementary Material Available: Complete characterization data for all compounds (8 pages). Ordering information is given on any current masthead page.

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Synthesis of Benzofurans from Oxygenated Phenoxyamines

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O-Aryloximes having various oxygenated substitution patterns have been converted to benzofurans, with implications toward natural product synthesis, through an extension of the Fischer indole type of synthesis. The effect of the substituent pattern in the benzene ring and the nature of the carbonyl derived portion of the oxime on benzofuranization were explored.

It is well established that *O*-aryloximes can be converted to benzofurans, presumably through a mechanism paralleling the one postulated for the Fischer indole synthesis.[1] This extension could prove useful in the synthesis of

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