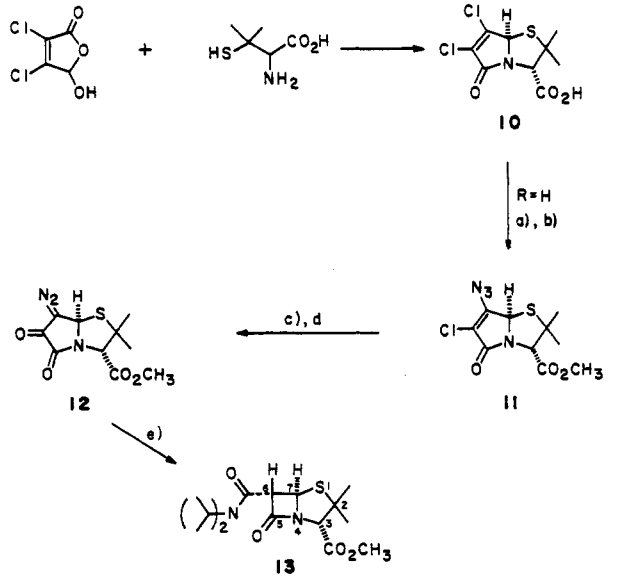
Scheme III



its derivatives since the 6,7-trans stereochemistry is desirable in these cases.

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Registry No. 1, 50343-26-5; **2a**, 86900-90-5; **2a**-ol, 86901-16-8; **2b**, 86900-91-6; **2c**, 86900-92-7; **3a**, 86900-93-8; **3b**, 86900-94-9; **3c**, 86900-95-0; **4a**, 86900-96-1; **4b**, 86900-97-2; **4c**, 86900-98-3; **5a**, 86900-99-4; **5b**, 86901-00-0; **5c**, 86901-01-1; *cis*-**8a**, 86901-02-2; *trans*-**8a**, 86901-03-3; *cis*-**8b**, 86901-04-4; *trans*-**8b**, 86901-05-5; *cis*-**8c**, 86901-06-6; *trans*-**8c**, 86941-19-7; *cis*-**9a**, 86901-07-7; *trans*-**9a**, 86901-08-8; *cis*-**9b**, 86901-09-9; *trans*-**9b**, 86901-10-2; *cis*-**9c**, 86901-11-3; *trans*-**9c**, 86941-20-0; (±)-**10**, 86901-12-4; (±)-**10** (methyl ester), 86901-13-5; (±)-**11**, 86901-17-9; (±)-**11** (amine), 86901-18-0; (±)-**12**, 86901-14-6; (±)-**13**, 86901-15-7; $LiC{\equiv}CC_6H_5$, 4440-01-1; $LiC{\equiv}CCH_2OCH_2C_6H_5$, 64080-63-3; $LiC{\equiv}C(CH_2)_3O$-THP, 85168-38-3; *dl*-penicillamine, 52-66-4; mucochloric acid, 766-40-5; diisopropylamine, 108-18-9.

Supplementary Material Available: Full experimental procedures and spectral data for compounds **2–5** and **8–13** (12 pages). Ordering information is given on any current masthead page.

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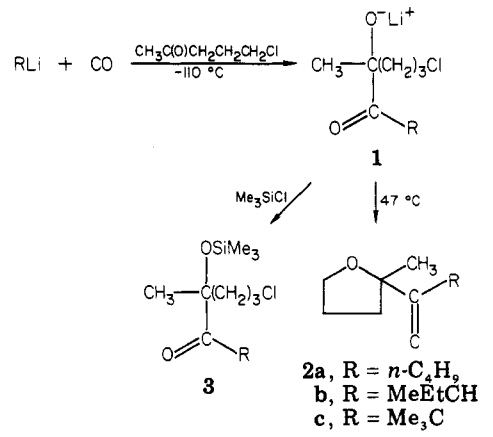
High-Yield Acyl Anion Trapping Reactions. Synthesis of Acyltetrahydrofurans

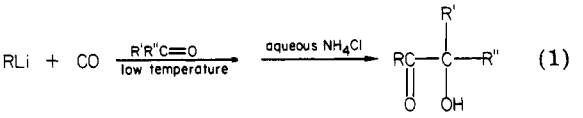
Summary: In situ generated acyllithium reagents add to the carbonyl function of lactones, usually with retention of the ring structure.

Sir: We have reported recently the nucleophilic acylation of ketones and esters by means of in situ generated

Scheme I



acyllithium reagents.[1] The latter were prepared by the carbonylation of alkyllithium reagents at low (−110 °C) temperature. Such reactions provided a facile, high-yield route to α-hydroxy ketones (eq 1). In the case of esters, α-diketones were the final products obtained.



(1)

In order to demonstrate that this novel chemistry may be applied to the synthesis of organic compounds other than simple α-hydroxy ketones and α-diketones, we have used our in situ direct nucleophilic acylation technique to prepare acyltetrahydrofurans by two different routes.

In one of these routes, the acyllithium reagent was generated at −110 °C in the presence of 2 molar equiv of 5-chloro-2-pentanone in a 4:4:1 THF/Et_2O/pentane solvent system.[2] The reaction mixture subsequently was heated at reflux (47 °C) for 2 h. The mixture was concentrated, treated with pentane to precipitate lithium salts, and filtered. The filtrate was concentrated and the residue examined by GLC. When *n*-butyllithium was the lithium reagent that was used, one product was present in 92% yield. This was identified as 2-pentanoyl-2-methyltetrahydrofuran (**2a**).[3] Scheme I summarizes the chemistry involved in this simple one-pot process. Intermediate **1** could be intercepted by adding trimethylchlorosilane to the reaction mixture at −110 °C to give **3**. Similar reactions in which *sec*-butyllithium and *tert*-butyllithium were used gave **2b** (95%) and **2c** (80%), respectively. This concept should be extendable to the preparation of other cyclic ethers containing an acyl function in the 2-position.

(1) Seyferth, D.; Weinstein, R. M.; Wang, W.-L. *J. Org. Chem.* **1983**, *48*, 1144.
(2) For details of the general procedure, see ref 1.
(3) Anal. Calcd for $C_{10}H_{18}O_2$: C,70.55; H, 10.66. Found: C, 70.46; H, 10.52. IR (film) ν(C=O) 1708 (s); ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, 3 H, CH_3 of the *n*-C_4H_9 group, J = 7.35 Hz), 1.21–1.35 (m, 5 H, contains a singlet at δ 1.30 for the $CH_3(H_c)$ group), 1.45–1.94 (m, 5 H), 2.19 (m, 1 H), 2.58 (complex m, 2 H, H_b (diastereotopic)), 3.96 and 3.82 (m, 1 H each, 2 H_a); ^{13}C NMR (gated decoupled, 67.5 MHz, $CDCl_3$) δ 13.8 (q, C_d, J = 124 Hz), 22.3, 23.8, 25.2, 25.7 (unresolved multiplets in the ^1H-coupled spectrum, includes the three CH_2s of the *n*-C_4H_9 group and the 2-methyl substituent), 35.0 (t, C_c, J = 129 Hz), 36.3 (t, C_c, J = 129 Hz), 68.7 (t, C_b, J = 145 Hz), 88.5 (s, C_a), 215 (s, C=O).

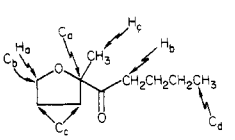
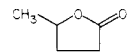
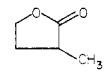
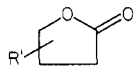


Table I. 1-(Trimethylsiloxy)-1-acyltetrahydrofurans (5) Obtained by Nucleophilic Acylation of Lactones[a]

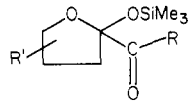
R in RC(O)Li	lactone (yield, %)		
			
n-C_4H_9	**5a**[b] (54)	**5b**[c] (64)	**5c**[d] (67)
MeEtCH	**5d** (59)	**5e**[e] (53)	**5f**[f] (72)
Me_3C	**5g** (81)	**5h**[g] (89)	**5i**[h] (64)

[a] The initial experiments were carried out with a 2:1 lactone/RLi ratio, although a 1:1 ratio was later employed. The 1:1 reactions are cleaner and proceed in approximately the same or in higher yield. [b] Also obtained was the ring-opened direct alkylation product n-$C_4H_9C(O)(CH_2)_3OSiMe_3$. [c] Obtained as a 2.4:1 ratio of isomers. [d] Only one isomer was observed (270-MHz ^1H NMR). [e] Obtained as a 2.6:1 ratio of isomers. [f] Isomer ratio could not be determined. [g] Obtained as a 1.4:1 ratio of isomers. [h] Obtained as a 17:1 ratio of isomers.

The reactions of in situ generated acyllithiums with lactones of the type **4** were found to proceed readily

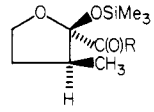


4, R = H, CH_3



5, R′ = H, CH_3

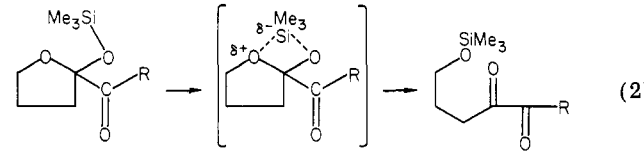
without ring opening to give products of the type **5** in good yield (Table I).[4] In the case of γ-valerolactone, two isomers were observed in the products from each acyllithium reagent (cf. Table I footnotes). The nucleophilic acylation of the α-methyl lactone in the case of n-$C_4H_9C(O)Li$ apparently gave only one isomer, and with $Me_3CC(O)Li$ one isomer was favored 17:1. In the α-CH_3 series, the major isomer probably is **6**, which results from attack of the acyllithium from the side opposite to the α-CH_3 group.



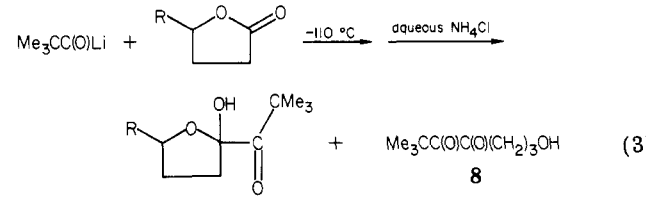
6

The colorless tetrahydrofuran derivatives of the type **5** were stable on distillation at reduced pressure (ca. 100 °C at 3–6 mmHg). However, on attempted isolation by means of preparative GLC, we obtained not the colorless **5** but rather bright yellow liquids. These were shown by their spectroscopic properties to be the 3-(trimethylsiloxy)propyl α-diketones, $RC(O)C(O)(CH_2)_3OSiMe_3$.[5] Apparently, the high injection port temperatures facilitated this isomerization.

The thermal isomerization of **5** to a single product occurred most readily when R = *tert*-butyl. For those cases we examined the kinetics of the ring-opening process and isolated pure $Me_3CC(O)C(O)CH_2CH_2CH(CH_3)OSiMe_3$ and $Me_3CC(O)C(O)CH(CH_3)CH_2CH_2OSiMe_3$.[5] The kinetics of the thermal isomerization of **5e**, **5f**, and **5i** were measured by analytical GLC and of **5d** by 270-MHz proton NMR spectroscopy. These isomerizations followed clean first-order kinetics, but those of **5a–c** were complicated by decomposition in part to unidentified products. This isomerization is an example of a [1,4] silyl migration from oxygen to oxygen (eq 2).[6] Attempts to prepare 3-(hydroxypropyl) α-diketones by the in situ nucleophilic acylation of lactones followed by hydrolysis of the reaction mixture gave a mixture of cyclic and acyclic products (eq 3) in both reactions which were carried out.



(2)



(3)

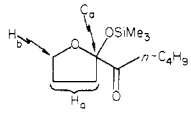
7

R = H, **7**:**8** = 1
R = CH_3, **7**:**8** = 2.8

These preliminary results have shown another useful application of *direct* nucleophilic acylation: the formation of acyl-substituted tetrahydrofurans. Furthermore, this work also has provided a new route to certain functionally substituted α-diketones. Both procedures used are capable of extension to other systems. Preliminary results, for instance, indicated that lactones of ring size other than five can undergo nucleophilic acylation. Our studies of direct nucleophilic acylation with in situ generated acyllithium reagents are continuing.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. We acknowledge also, with thanks, the award of a fellowship to R. M. Weinstein by the Rhône-Poulenc Co.

(4) For example, the product of the reaction of n-$C_4H_9C(O)Li$ and γ-butyrolactone (after silylation) was characterized as follows. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 59.40; H, 9.89. IR (film) ν(C=O) 1730 (s); NMR (90 MHz, C_6D_6) δ 0.18 (s, 9 H, $OSiMe_3$), 0.79 (t, 3 H, CH_3 of n-C_4H_9 group, J = 5.8 Hz), 1.10–2.25 (m, 8 H, H_a + $CH_3CH_2CH_2CH_2C(O)$), 2.5 (center of multiplet, 2 H, $CH_2C(O)$; diastereotopic protons make this m complex), 3.2–3.7 (m, 2 H, H_b); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 1.13 ($SiMe_3$), 13.86 (CH_3 of C_4H_9 group), 22.32, 24.64, 25.70, 36.07, 36.48 (CH_2s of the ring and the n-C_4H_9 group), 69.5 (OCH_2CH_2), 107.3 (C_a), 208.1 (C=O).



(5) For example, **5i** gave $Me_3CC(O)C(O)CH(CH_3)CH_2CH_2OSiMe_3$, a yellow liquid. Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.72; H, 10.16. IR (film) ν(C=O) 1700 (s); ^1H NMR (270 MHz) δ 0.07 (s, 9 H, $SiMe_3$), 1.06 (d, 3 H, $CHCH_3$), J = 7.28 Hz), 1.22 (s, 9 H, CMe_3), 1.49 and 1.92 (m, 6 lines each, 2 H, CH_2 β to C=O, diastereotopic protons), 3.25 (m, 1 H, 6 lines, $CHCH_3$), 3.57 (t, 2 H, CH_2OSi), J = 6.74 and 6.18, different J due to diastereotopic H_a).

(6) Such rearrangements have been shown to occur in the epoxidation of enol silyl ethers[7] or ketene bis(trimethylsilyl) acetals.[8]

(7) (a) Brook, A. G.; Macrae, D. M. *J. Organomet. Chem.* **1974**, *77*, C19. (b) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.

(8) Rubottom, G. M.; Marrero, R. *J. Org. Chem.* **1975**, *40*, 3783.

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