

Alternatively, addition of lithium dimethylcopper to 10 in ether afforded 11 and 12 in a 1/4.5 mixture, this time favoring 8-*epi*-methyl nonactate (12), the ^1H NMR spectrum of which was identical with one of an authentic sample.⁹ This result is in contrast to the 1/1 mixture previously obtained for the same reaction carried out in pentane.^{3j} The exact nature of this interesting solvent effect is not clear at the present time.

In summary, racemic methyl nonactate and 8-*epi*-methyl nonactate have each been prepared with good efficiency and high stereospecificity. The three diastereoisomeric relationships of methyl nonactate were introduced with stereoselectivities of 32:1, 50:1, and 24:1.

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Supplementary Material Available: A complete experimental section with synthetic procedures for all compounds in this work (9 pages). Ordering information is given on any current masthead page.

S. W. Baldwin,* J. M. McIver

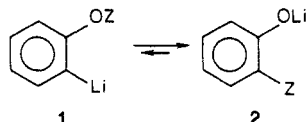
Paul M. Gross Chemical Laboratory
Duke University
Durham, North Carolina 27706

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The Metal-Promoted Fries Rearrangement[†]

Summary: Upon reaction with *sec*-butyllithium at low temperature, *o*-bromophenyl esters 3 undergo an intramolecular acyl migration to produce, after hydrolysis, the corresponding *o*-hydroxy ketones 4.

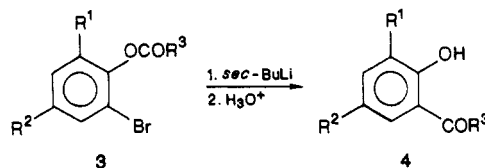
Sir: The O→C migration of silicon in 1 ($Z = \text{R}_3\text{Si}$) to form the corresponding lithium phenoxide 2 is a well-documented process.¹ This migration occurs when group Z (as



with R_3Si) is an electrophilic center with the capacity to serve as a bridge to effectively transport the negative charge from the aromatic carbon to the phenolic oxygen. Such a requirement is met when $Z = \text{acyl}$, and this has prompted our examination of the corresponding aryl ester → *o*-hydroxy ketone transformation, which can formally be viewed as a metal-promoted Fries rearrangement.^{2,3}

We now wish to report that the Fries reaction can indeed be metal-promoted to afford, under the proper reaction conditions, good yields of *ortho*-specific acyl migration products (Table I).^{4,5} For example, *o*-bromophenyl pivaloate (3c) was treated at -95°C with *sec*-butyllithium (1.1 equiv, 4:1:1 THF/ether/hexane, 0.25 M) and stirred for 30 min. After an additional 30 min at -78°C , the mixture was hydrolyzed with saturated NH_4Cl . GC analysis showed the formation of *o*-hydroxypivalophenone (4c)⁶ in 76% yield.⁷ The only other products detected were phenyl pivaloate and the starting aryl ester 3c, each present in ca. 5% yield. It is significant that none of the regioisomeric *p*-hydroxypivalophenone is found in this reaction, since *ortho*/*para* mixtures are known to be commonplace with the Fries rearrangement.⁸ In fact, treat-

Table I. Yields of *o*-Hydroxy Ketones 4 Derived from *o*-Bromophenyl Esters 3



entry	R ¹	R ²	R ³	yield (%) of 4 ^d GC (isolated)
a ^a	H	H	Et	17
b ^a	H	H	<i>i</i> -Pr	62 (54)
c	H	H	<i>t</i> -Bu	76 (68)
d ^{a,b}	H	H	Ph	7
e	H	H	1-adamantyl	(81)
f	H	H	<i>tert</i> -pentyl	91 (85)
g	H	Me	<i>t</i> -Bu	71 (62)
h	H	Me	<i>tert</i> -pentyl	84 (76)
i	H	H	C(Me) ₂ CH ₂ Cl	(49)
j ^a	Me	Me	Et	31 (17)
k ^a	Me	Me	<i>i</i> -Pr	72 (61)
l ^{a,c}	<i>t</i> -Bu	<i>t</i> -Bu	Me	52 (43)

^a Yield (GC) of residual starting ester: 3a (39%); 3b (30%); 3d (31%); 3j (39%); 3k (24%); 3l (9%). ^b Major byproduct was *di*-*sec*-butylphenylcarbinol (30%). ^c 2.0 equiv of *sec*-butyllithium was used. ^d The IR and ^1H and ^{13}C NMR data of the isolated compounds were consistent with the assigned structure. In addition, all new compounds have yielded satisfactory high-resolution mass spectra.

ment of phenyl pivaloate with AlCl_3 (1.2 equiv, $\text{ClCH}_2\text{C}-\text{H}_2\text{Cl}$, reflux, 18 h) afforded, besides phenol (65%), *p*-*tert*-butylphenol (25%) as the only product derived from electrophilic aromatic substitution.^{9,10} None of the *o*- or *p*-hydroxypivalophenones were found by GC examination. Thus, a distinct advantage of the metal-promoted Fries

(1) Simchen, G.; Pfletschinger, J. *Angew. Chem., Int. Ed. Engl.* 1976, 15, 428. Habich, D.; Effenberger, F. *Synthesis* 1979, 841 and references contained therein. Billedeau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* 1983, 24, 4515.

(2) Although a recent paper has briefly touched on this rearrangement, extremely poor yields of acyl migration products were obtained from the pair of examples described: Hellwinkel, D.; Lammerzahn, F.; Hofmann, G. *Chem. Ber.* 1983, 3375. The only other precedent to our work using a carbonyl as the migrating unit is the transformation 1 → 2 with $Z = \text{CONR}_2$: Sibi, M. P.; Snieckus, V. *J. Org. Chem.* 1983, 48, 1935. Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* 1985, 50, 5436.

(3) (a) Interesting analogies to this reaction include the acyl migration occurring from a benzylic carbon to an aromatic carbon atom observed under strenuous reaction conditions,^{3b} the Cr(II)-mediated conversion of *o*-*O*-acylbenzyl bromides into *ortho*-hydroxybenzyl ketones,^{3c} and the conversion of phenyl tetrahaloethyl ethers to the corresponding 1-(2-hydroxyphenyl)alkynes.^{3d} (b) Dyllick-Brenzinger, R. A.; Strothers, J. B. *J. Chem. Soc., Chem. Commun.* 1979, 108. (c) Ledoussal, B.; Gorgues, A.; Le Coq, A. *J. Chem. Soc., Chem. Commun.* 1986, 171. (d) Subramanian, R.; Johnson, F. *J. Org. Chem.* 1985, 50, 5430.

(4) The fact that the metal-promoted Fries reaction provides good yields of *o*-hydroxy ketones 4 from esters 3 possessing 2°-substituted acyl moieties (e.g., 3b,k) demonstrates that metal-halogen exchange with subsequent acyl migration occurs in preference to enolization.

(5) No clear advantage in yield or purity of the ketones 4 was gained by substituting bromine in 3 with iodine, or by using alternative organolithium reagents. However, in most cases a 10–20% increase in yield was realized by lowering the reaction temperature from -78°C to -95°C .

(6) Basil, B.; Coffee, E. C. J.; Gell, D. L.; Maxwell, D. R.; Sheffield, D. J.; Wooldridge, K. R. H. *J. Med. Chem.* 1970, 13, 403.

(7) The attempted direct *ortho*-metalation of phenyl pivaloate with *sec*-butyllithium/TMEDA (-95°C) provided the acyl migration product 4c in only 6% yield.

(8) Blatt, A. H. *Org. React. (N.Y.)* 1942, 1, 342. Gerecs, A. in *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; J. Wiley & Sons: New York, 1964; Vol. 3, Pt. 1, pp 499–533.

(9) Similar results from the attempted Fries rearrangement of phenyl pivaloate have been observed: Martin, R. *Bull. Soc. Chim. Fr.* 1979, 373.

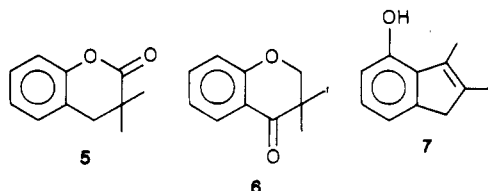
(10) Acylium ions which are highly hindered by branching at the α -carbon, such as pivaloyl cation, often furnish only alkylated benzenes in Friedel-Crafts reactions due to the loss of carbon monoxide: Olah, G. A.; Germain, A.; White, A. M. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1976; Vol. 5, p 2123.

[†] Dedicated to Prof. George Zweifel, an inspiring teacher and scientist, on the occasion of his 60th birthday.

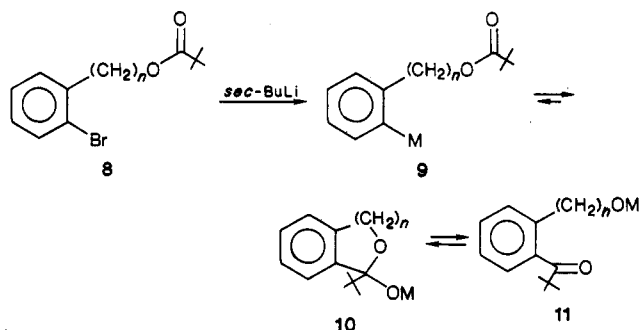
reaction vs. the classical Fries is the ability of the former to accommodate hindered acyl groups.

Cross-over reactions were utilized to determine the nature of this acyl migration. Thus, reaction of a mixture of **3c** and **3h** (1 equiv each) with *sec*-butyllithium (2 equiv) under the standard conditions yielded only **4c** and **4h**, with none of the corresponding intermolecular reaction products **4f** and **4g** present by GC analysis. Likewise, the similar reaction of a mixture of **3f** and **3g** with *sec*-butyllithium afforded only **4f** and **4g**. It may, therefore, be concluded on the basis of these experiments that the acyl migration step in this reaction is an *intramolecular* process. Paralleling these results is the fact that the reaction of *p*-bromophenyl pivaloate with *sec*-butyllithium under identical conditions provided only 3% of the acylation product *p*-hydroxypivalophenone, further demonstrating that intermolecular acylation is not a facile occurrence.

Interestingly, the reaction of *o*-bromophenyl 3-chloro-2,2-dimethylpropionate (**3i**) with *sec*-butyllithium furnished the corresponding acyl migration product **4i** without any trace of the dimethylcoumarin derivative **5**¹¹ thereby illustrating the inability of Parham-type cyclization¹² to favorably compete with the metal-promoted Fries rearrangement. Treatment of **4i** with sodium hydride (1.5 equiv, THF, 60 °C, 1 h) afforded the 3,3-dimethyl-4-chromanone (**6**) in essentially quantitative yield, while sequential reaction of **4i** with borane (2.1 equiv, THF, 0 °C, 30 min) and aluminum chloride (2.1 equiv, ClCH₂C-H₂Cl, 0 °C, 30 min) cleanly produced the 4-hydroxy-2,3-dimethylindene (**7**) (79%),¹³ this establishes efficient, new synthetic entries into these bicyclic systems.



We have also examined the propensity for the series of pivaloates **8**, having the ester functionality separated from the aromatic nucleus by a carbon chain, to participate in this acyl migration reaction. Baldwin's rules¹⁴ predict that *exo*-trig cyclizations such as **9** → **10** should be favored when $n = 0-3$. Accordingly, we have found that this novel rearrangement does indeed occur readily for these substrates. Interestingly, however, utilization of the pivaloate **8** (where $n = 1$) in the reaction depicted above (carried out identically to the transformation **3** → **4** detailed earlier) furnished only **10** ($M = H$) upon hydrolysis (86% yield); no trace of **11** ($M = H$) was detected.¹⁵ Conversely, the same process with $n = 2$ provided the acyl migration adduct as an approximately equal mixture of tautomers **10** and **11** ($M = H$, 77% yield),¹⁶ whereas the pivaloate **8** with $n = 3$ afforded only the hydroxy ketone **11** ($M = H$, 58% yield). As expected, the reaction of **8** ($n = 4$) with *sec*-



butyllithium afforded the respective migration product **11** in low yield ($M = H$, 16%).¹⁷

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Supplementary Material Available: Experimental findings for **4e**, **4f**, **4h**, **4i**, **4k**, **5**, **6**, **7**, **9** ($n = 0$, $M = SiMe_3$), **10** ($n = 1$ and 2 , $M = Me$), and **11** ($n = 3$ and 4 , $M = H$) (3 pages). Ordering information is given on any current masthead page.

(17) We attempted to elucidate the nature of the intermediate for the transformation **8** → **11** where $n = 0$ by carrying out the reaction between *o*-bromophenyl pivaloate and *sec*-butyllithium in the presence of chlorotrimethylsilane (5.0 equiv, -95 °C).¹⁸ Examination of the reaction solution revealed none of the "trapped intermediate" **10** ($n = 0$, $M = SiMe_3$) or even the *O*-silylated acyl migration derivative **11** ($n = 0$, $M = SiMe_3$). Instead, the sole product formed in the reaction was **9** ($n = 0$, $M = SiMe_3$, 92% yield by GC), derived from silylation of the initially produced aryllithium species.¹⁹ Hence, while the metal-promoted Fries rearrangement appears to be a facile process (vide supra), the intermediate aryllithium **9** ($n = 0$, $M = Li$) obtained from metal-halogen exchange evidently has a finite lifetime which enables it to be trapped with a reactive electrophile such as chlorotrimethylsilane before acyl migration can occur.

(18) The reaction between esters and alkylolithiums in the presence of chlorotrimethylsilane has been found to produce high yields of the corresponding "Me₃Si-trapped" ketals: Cooke, M. P., Jr. *J. Org. Chem.* 1986, 51, 951.

(19) An *in situ* trapping of aryllithium derivatives with chlorotrimethylsilane has previously been reported: Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* 1983, 105, 6155.

Joseph A. Miller

The Procter & Gamble Co.
Miami Valley Laboratories
Cincinnati, Ohio 45247

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(11) Prepared from dihydrocoumarin via two successive deprotonation/alkylation reactions using LDA and MeI.

(12) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* 1982, 15, 300.

(13) The regiochemistry of **7** was confirmed by ¹H and ¹³C NMR (500 MHz) decoupling experiments.

(14) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* 1976, 734, 738.

(15) The formation of the essentially pure hemiketal **10** ($n = 1$, $M = H$) is in contrast to the tautomeric equilibrium mixtures of other substituted 1-hydroxyphthalans and hydroxy ketones previously reported: Berner, E. *Acta Chem. Scand., Ser. B* 1982, 36, 729. Smith, J. G.; Dibble, P. W. *Tetrahedron* 1984, 1667.

(16) Both the hemiketal **10** ($n = 1$, $M = H$) and the mixture of **10** and **11** ($n = 2$, $M = H$) were transformed into the pure corresponding ketals **10** ($M = Me$, $n = 1$: 93% and $n = 2$: 95% isolated yields) by treatment with methanol/cat. TsOH (25 °C, 1 h).

(1) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill, New York, 1962; pp 341-346.

(2) Kwie, W. W.; Gardiner, W. C., Jr. *Tetrahedron Lett.* 1963, 405.

(3) Brown, W. G.; Jankowski, S. *J. Am. Chem. Soc.* 1966, 88, 233.