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Use of Acid Fluorides Increases the Scope of the Reductive Acylation of Esters

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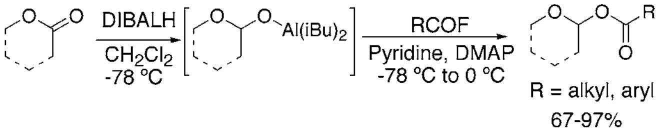
ABSTRACT



The use of acyl fluorides in the Rychnovsky reductive acylation of esters allows a variety of esters to be converted to their corresponding α-acyloxy ethers in good to excellent yields, without the need to sacrifice an extra equiv of carboxylic acid functionality.

Rychnovsky and co-workers have recently developed a protocol for the in situ acylation of an aluminum alkoxide derived from DIBAL-H reduction of an ester or lactone.[1] The advantage of this method is that kinetic trapping of the hemiacetal prevents its decomposition into aldehyde and alcohol constituent parts. Currently, however, only symmetrical acid anhydrides participate successfully in this transformation.

Recently, we have developed a Lewis acid mediated stereoretentive [1,3] rearrangement of vinyl acetals, wherein the selectivity is controlled by tight ion pairing.[2] As part of an effort toward the synthesis of the clavosolides,[3] we envisioned using the reductive acylation of a dioxanone to afford the requisite acyl acetal. Although Rychnovsky and co-workers have reported the successful use of only acetic anhydride as acylation reagent, we have found that other symmetrical anhydrides react well under their conditions.[2b] However, we ultimately hoped to couple two reasonably functionalized partners by this method without sacrificing a full equivalent of acid by the use of the symmetrical anhydride. Herein, we disclose our efforts toward this goal.

We initiated our screen with a variety of common acylation reagents employing the 1,3-dioxolan-4-one **1**[4] as a model substrate. Our results are summarized in Table 1. When the pivaloyl mixed anhydride was used, the desired product was isolated in 50% yield (entry 1).[5,6] The use of the mixed anhydride derived from isobutyl chloroformate resulted in no acylation product (entry 2). Pyridyl esters,[7] pyridyl thioesters,[7] *N*-hydroxysuccinimide esters, and acyl imidazoles proved equally ineffective as anhydride surrogates (entries 3−6). The use of acid chlorides afforded poor yields of desired product (30−40%, entry 7).[8] In contrast, the use of benzoic anhydride provided the desired acylation product in 95% yield (entry 8).

The inefficiency of acid chlorides in the reaction is difficult to reconcile from a reactivity standpoint. We speculate that the byproduct in the reaction, DIBAL-Cl, may be decomposing an intermediate or product or altering the reaction in some other way. Indeed, a control experiment revealed that 1 equiv

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[1] (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem*. **1996**, *61*, 8317. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem*. **2000**, *65*, 191.

[2] (a) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720. (b) Zhang, Y.; Rovis, T. *Tetrahedron* **2003**, *59*, 8979.

[3] (a) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod*. **2002**, *65*, 386. (b) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. *J. Nat. Prod*. **2002**, *65*, 1303.

[4] Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem*. **2000**, *65*, 6283.

[5] We speculated that the low conversion is due to the bulk of this reagent. To probe this issue, we attempted the one-pot reduction/acylation with trimethylacetic anhydride, which afforded the desired product **3e** in less than 30% yield under identical reaction conditions, consistent with Kiyooka's observations (ref 6), thereby supporting our conjecture.

[6] Kiyooka found that increasing the bulk of the silylating reagent from TMSOTf to TBDMSOTf resulted in a poor efficiency in the reductive silylation of esters; see: Kiyooka, S.-I.; Shirouchi, M.; Kaneko, Y. *Tetrahedron Lett.* **1993**, *34*, 1491.

[7] Kim, S.; Lee, J. I. *J. Org. Chem*. **1984**, *49*, 1712.

[8] Rychnovsky and co-workers have also noted this effect (personal communication).

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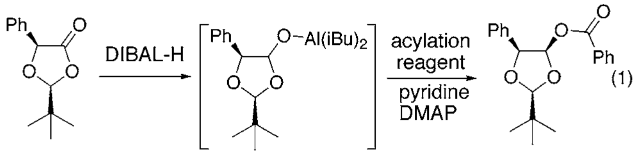
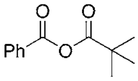
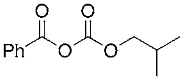
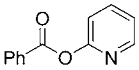
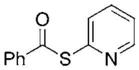
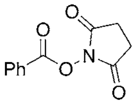
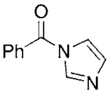
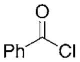
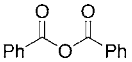
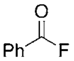
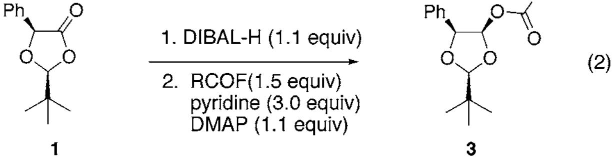
Table 1. Initial Screen of Acylation Reagent

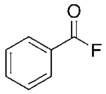
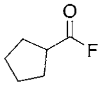
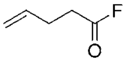
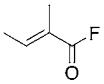
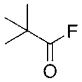
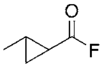


entry[a]	acylation reagent	yield[b]
1		52%
2		NR[c]
3		NR[c]
4		NR[c]
5		NR[c]
6		NR[c]
7		30 - 40%
8		95%
9		94%

[a] All reactions conducted in CH_2Cl_2 using 1.1 equiv of DIBAL-H, 3 equiv of pyridine, 1.1 equiv of DMAP, and 1.5 equiv of acylation reagent. [b] Isolated yield. [c] No acylation product isolated.

Table 2. Effect of Structure of Acyl Fluoride



entry[a]	acyl fluoride[b]	product	yield (%)[c]
1		**3a**	94
2		**3b**	97
3		**3c**	92
4		**3d**	87
5		**3e**	92
6		**3f**	67

[a] All reactions conducted in CH_2Cl_2 using 1.1 equiv of DIBAL-H, 3 equiv of pyridine, 1.1 equiv of DMAP, and 1.5 equiv of RCOF. [b] All acyl fluorides except benzoyl fluoride were prepared from the corresponding acids using HF•Py and DCC.[13] [c] Isolated yield.

of DIBAL-Cl had a deleterious effect on the yield in a reaction utilizing an anhydride as the acylation agent.[9] We turned our attention to acid fluorides as acylation agents in order to benefit from acid halide reactivity while avoiding the Lewis acidity of the aluminum halide byproduct. Although little is known about the dialkyl aluminum fluorides, it has been suggested that they are not as Lewis acidic but are much more prone to form aggregates relative to dialkylaluminum chloride.[10,11] Acyl fluorides have been frequently used in peptide synthesis, and their reactivity has been compared to that of activated esters.[12] In addition, they are easily prepared from the corresponding acid,[13] acid chloride,[14] or acid anhydride.[15] In the event, the use of benzoyl fluoride in the reductive acylation provided **3a** in a yield comparable to that achieved with benzoic anhydride, entry 9 vs entry 8.[16]

To delineate the scope of the reaction with acyl fluorides, the DIBAL-H reduction and acylation of dioxolanone **1** was tested using a variety of acyl fluorides. The results are summarized in Table 2. The reactions were carried out with 1.1 equiv of DIBAL-H at −78 °C for ca. 2 h in CH_2Cl_2. The intermediate aluminum hemiacetal was then treated with 3 equiv of pyridine, 1.1 equiv of DMAP, and 1.5 equiv of acyl fluoride at −78 °C, and the resulting mixture was allowed to warm slowly to ca. 15 °C over 12 h. After an aqueous workup, the α-acetoxy ether was isolated by silica gel chromatography. The use of acyl fluorides bearing aryl, alkyl, vinyl, or cyclopropyl groups gave good to excellent yields of isolated products. Impressively, the pivalate ester **3e** could be isolated in 92% yield when the bulky trimethylacetyl fluoride was employed, entry 5.

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[9] Control experiments also showed that the acylation product is stable to DIBAL-Cl under the reaction conditions.

[10] (a) Laubengayer, A. W.; Lengnick, G. F. *Inorg. Chem.* **1966**, *5*, 503. (b) Me_2AlF is a tetramer in solution up to 100 °C.; see: Gundersen, G.; Haugen, T.; Haaland, A. *J. Organomet. Chem.* **1973**, *54*, 77.

[11] (a) Weidlein, J.; Krieg, V. *J. Organomet. Chem.* **1968**, *11*, 9. (b) Oishi, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1445.

[12] Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bieneri, M. *Acc. Chem. Res.* **1996**, *29*, 268.

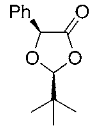
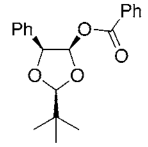
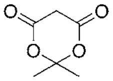
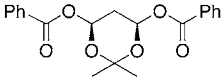
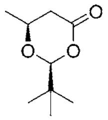
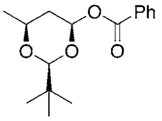
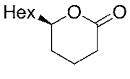
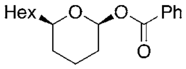
[13] Chen, C.; Chien, C.-T.; Su, C.-H. *J. Fluorine Chem.* **2002**, *115*, 75.

[14] Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872. Also see ref 13.

[15] Olah, G. A.; Kuhn, S. J. *J. Org. Chem.* **1961**, *26*, 237.

[16] The use of acid fluorides simplifies the workup by avoiding emulsions, which in our hands are often observed in reactions that use anhydrides as acylation partners.

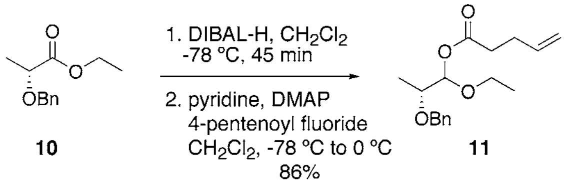
Table 3. DIBAL-H Reductive Acylation of Lactones with Benzoyl Fluoride

entry[a]	starting ester	product	yield (%)[b]	ratio[c]
1	 **1**	 **3a**	94	> 10:1
2[d]	 **4**	 **5**	93	> 10:1
3	 **6**	 **7**	94	> 10:1
4	 **8**	 **9**	83	> 10:1

[a] All reactions conducted in CH_2Cl_2 using 1.1 equiv of DIBAL-H, 3 equiv of pyridine, 1.1 equiv of DMAP, and 1.5 equiv of PhCOF, unless otherwise stated. [b] Isolated yield. [c] Ratios were determined by ^1H NMR analysis. [d] Reaction conducted using 2.2 equiv of DIBAL-H, 6 equiv of pyridine, 2.2 equiv of DMAP, and 3.0 equiv of PhCOF.

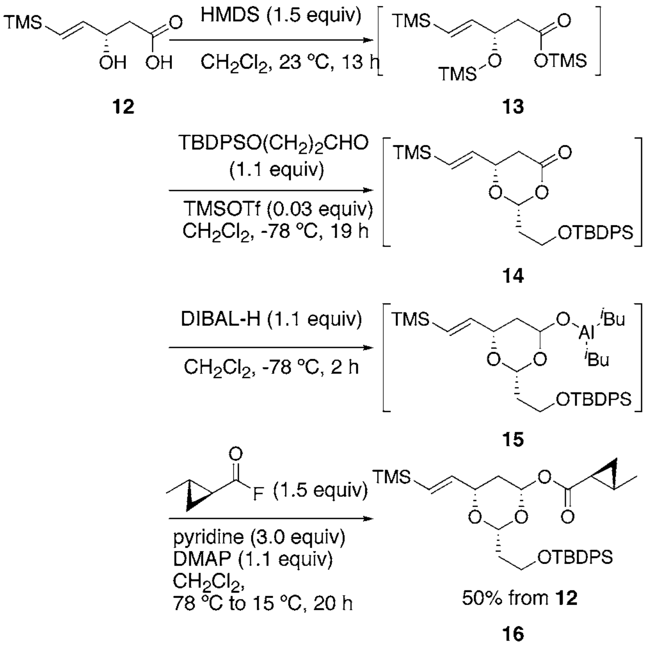
A variety of simple cyclic esters were also used to investigate the scope of this transformation. The results are summarized in Table 3. Rychnovsky has noted that none of the desired product is isolated when Meldrum's acid and acetic anhydride are used.[1a] Under our conditions, the desired double reduction/acylation product **5** could be isolated as a white solid in 93% yield when Meldrum's acid was exposed to 2.2 equiv of DIBAL-H followed by treatment with 3 equiv of benzoyl fluoride, entry 2. The 1,3-dioxan-4-one **6** gave the desired product **7** in 94% yield with good diastereoselectivity, entry 3. Treatment of undecanoic δ-lactone with DIBAL-H followed by reaction with benzoyl fluoride gave the desired product **9** in 83% yield, entry 4.

Good yields can also be achieved in the reductive acylation of acyclic esters[1b] when acyl fluorides are used. Treatment of the benzyl-protected ethyl lactate **10** with DIBAL-H at −78 °C for 45 min followed by sequential addition of pyridine, DMAP, and 4-pentenoyl fluoride gave the desired product **11** in 86% yield (eq 3).



(3)

Scheme 1



The use of this protocol allows the efficient coupling of two functionalized partners. Indeed, we have developed conditions that convert a β-hydroxy acid to the acyl acetal without isolation of intermediates (Scheme 1). Bis-silylation of β-hydroxy acid **12** followed by removal of volatiles sets the stage for a condensation with β-(*tert*-butyldiphenylsiloxy) propionaldehyde. The resulting1,3-dioxanone **14** was treated with DIBAL-H followed by addition of pyridine, DMAP, and 2-methyl-cyclopropane carbonyl fluoride. The desired ester **16** is isolated in 50% overall yield from the acid.

In conclusion, acyl fluorides have been shown to be efficient acylation reagents in the one-pot reductive acylation of esters. Their use extends the scope of this transformation and allows complex fragments to be assembled in an efficient manner. The application of this methodology to complex molecule total synthesis is currently underway.

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Supporting Information Available: Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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