Tetrahedron Letters, Vol. 33, No. 6, pp. 757-760, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

Acid Lability of Allylic Esters: Use of Methallyl Esters as Acid-Labile Protecting Groups for Carboxylic Acids

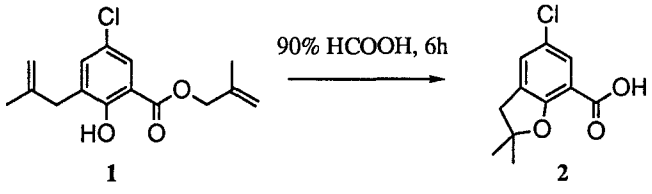
Christopher R. Schmid

Chemical Process Research and Development
Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, IN 46285-4813

Key Words: Methallyl Ester; Protecting Group; Formic Acid; Carboxylic Acids; Ester Hydrolysis

Abstract: *Substituted allylic esters are cleaved in refluxing 90% formic acid to afford carboxylic acids. The scope and generality of the reaction is investigated, and several examples using methallyl esters as an acid-labile protecting group for carboxylic acids are presented.*

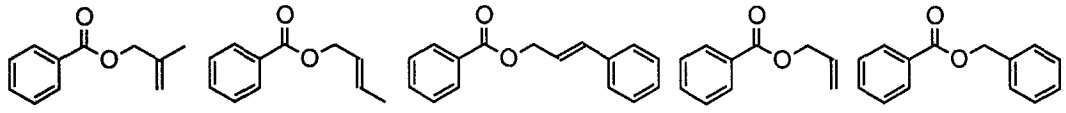
Recently we noted an unexpected propensity for acidic cleavage of the methallyl ester portion of compound **1**, which upon treatment in refluxing formic acid delivered cyclized carboxylic acid **2**. Intrigued with this observation, we decided to explore the generality of the phenomenon, and disclose our findings in this Letter.



1 **2**

While acid-labile protecting groups (*t*-butyl, *p*-methoxybenzyl, trityl) are routinely employed in synthesis for the deprotection of carboxylic acids,[1] there appears to be no literature precedent for the use of allylic esters as acid-labile protecting groups,[2] even though the relative stabilities of the allylic, benzylic and tertiary carbonium ions are qualitatively regarded as approximately equal. Using benzoic acid as a test substrate, allylic esters were prepared using conventional techniques (K_2CO_3, allylic halide, DMF, or allylic alcohol, pyridine, CH_2Cl_2, benzoyl chloride) in high yield and purity. The esters were then subjected to cleavage conditions of refluxing 90% formic acid and the reactions monitored by NMR, TLC and HPLC. The results revealed some unexpected trends. The methallyl (**3**), crotyl (**4**) and cinnamyl (**5**) esters were all completely removed within 2 h under these conditions. Surprisingly, simple allyl benzoate **6** was recovered unchanged from the reaction after 16 h;

similarly, benzyl ester **7** reacted sluggishly, showing ca. 40% conversion at 4 h. Control experiments with ethyl benzoate demonstrated no cleavage under the reaction conditions for 16 h. Under less severe conditions (80 °C), methallyl and cinnamyl benzoates showed approximately equal half lives (35-40 min). Small amounts



3 **4** **5** **6** **7**

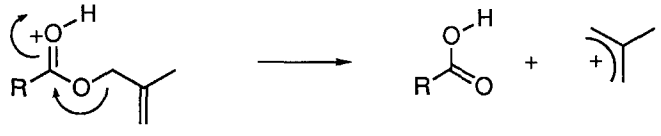
of water in the system proved synthetically advantageous; reactions run in 98% formic acid proceeded satisfactorily (86% in-situ yield of benzoic acid from **3**), but by-products were not volatilized, leading to product of lower overall potency. In contrast, use of 90% formic acid afforded a similar yield (91%) of substantially higher potency material (92% vs 69%).

The acid conditions required to effect cleavage were also briefly investigated. Methallyl benzoate **3** was stable to conditions normally employed to cleave *t*-butyl esters (room temperature, trifluoroacetic acid (TFA), CH_2Cl_2),[3] as well as reaction with 1.1 equiv of TFA at reflux in 1,2-dichloroethane. Neat TFA at reflux was effective for ester cleavage; addition of 10 vol-% of water again proved beneficial, and benzoic acid was produced in 88% yield and 87% potency. Starting material was recovered unchanged from refluxing glacial acetic acid after 16h.

Since the methallyl ester hydrolysis reaction using 90% formic acid gave high potency product directly, we explored the use of the methallyl ester as an acid-labile protecting group. Our findings are summarized in the Table.[4] As can be seen, both aliphatic and aromatic acid methallyl esters were smoothly deprotected. Interestingly, we did not observe a substantial rate difference between methally benzoate **3** and methallyl *p*-nitrobenzoate (entries 1 and 2); both deprotections were completed within 2 h. Acid-catalyzed or promoted processes can be carried out concurrently with deprotection (entry 3), thereby eliminating a separate deprotection step. Methallyl esters have been shown to undergo cleavage with Pd(0) methodology;[5] moreover, **3** was easily saponified (H_2O, MeOH, NaOH, 87%). Thus the methallyl ester provides a wider range of options (acid, base, transition metal) for deprotection than most other esters.

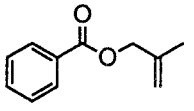
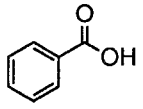
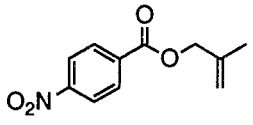
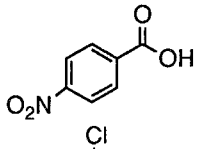
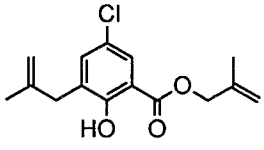
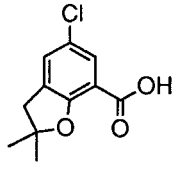
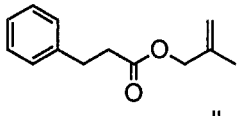
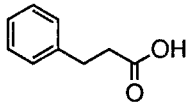
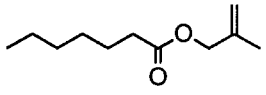
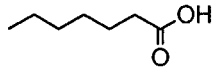
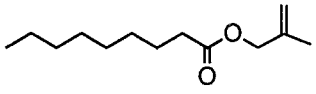
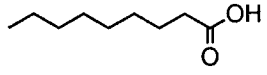
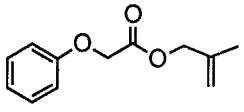
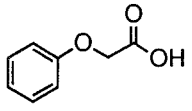
While no systematic studies have been undertaken, the pattern of reactivity exhibited by the various allylic esters, coupled with the non-reactivity of conventional esters under these conditions, suggests a simple allylic ionization of protonated material as the operating mechanism (Scheme). The propensity for reaction of substituted or extended allylic systems over simple allyl or benzyl might then be explained by the increased allylic cation stability provided by alkyl substitution or conjugation.[6,7] This postulate also suggests that

Scheme



other methallyl-based protecting groups (e.g. carbonates, carbamates and ethers) might also display acid lability and find use in synthesis; we intend to pursue these opportunities.

Table: Cleavage of Methallyl Esters to Carboxylic Acids[a]

Entry	Substrate	Product	Yield(%)[b]
1			87
2			89
3			80[c]
4			91
5			84
6			92
7			95

a. Conditions: Ratio substrate:formic acid:water 1:10:1, reflux 3 h. Reactions judged complete by NMR.
b. Isolation by concentration, reconstitution in diethyl ether, extraction (2x) with 1 N NaOH, acidification and extraction/concentration of product. c. Isolation and purification by recrystallization from toluene.

The methallyl ester will find service in synthetic strategies requiring deprotection concomitant with other acid-catalyzed chemistry, or in those instances where flexibility in deprotection protocols may be required. Given its moderate acid lability and the relatively aggressive conditions for its deprotection, it is also well suited for use in differentially protected compounds, as other protected functionality (*t*-butyl esters, THP and silyl ethers, etc) are easily deprotected under conditions where the methallyl ester is stable.

References and Notes

1. Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York. 1981; pp. 152-192.
2. Hydrolysis of esters under highly acidic conditions has been reported: Loev, B. *Chem. Ind.*, **1964**, 193-194.
3. Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.*, **1977**, *99*, 2353.
4. Reported yields refer to isolated homogeneous compound exhibiting satisfactory NMR, IR and combutstion analyses. We thank Molecular Structure Research, Lilly Research Laboratories, for providing IR spectra and combustion analyses on the Table compounds.
5. Allylic esters (including a methallyl example) have been cleaved with Pd(0) in the presence of acid: Hey, H.; Arpe, H.-J. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 928-929. For use of soluble Pd(0) in deprotection of allylic esters and other functionality, see also: (a) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587-590. (b) Kunz, H.; Waldmann, H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 71.
6. For a discussion on the stabilization effects of conjugation on olefins, see: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons: New York. 1976; ch. 4.
7. It is interesting to speculate on the lack of rate difference between methallyl benzoate **3** and methallyl *p*-nitrobenzoate. If protonation of substrate represents a fast and reversible preequilibrium to rate-determining sigma bond rupture/allylic ionization, the usually pronounced effects of *p*-nitro substitution might be mitigated, since the methallyl group effectively leaves a neutral molecule in the rate-determining step in both cases. The experiments performed would not distinguish relatively small rate differences between these two substrates.

(Received in USA 15 October 1991)