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In situ synthesis of 2-allyloxy-1-methylpyridinium triflate for the allylation of carboxylic acids

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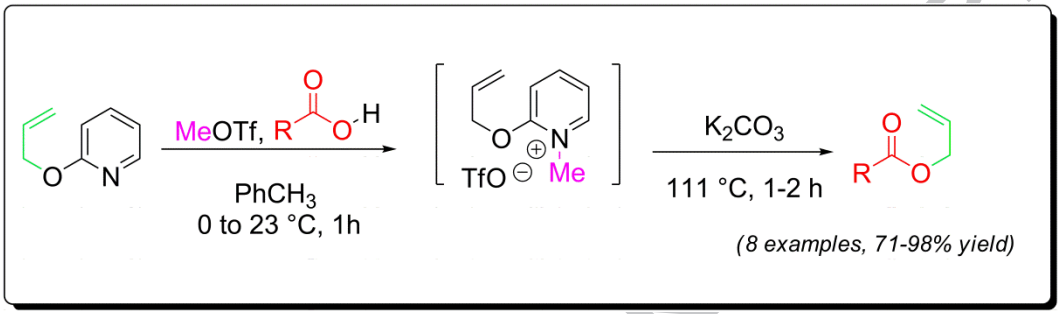


Abstract

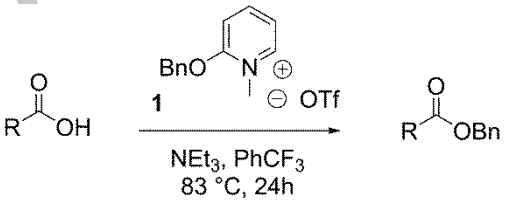
2-allyloxypyridinium triflate is formed in situ by treating a mixture of 2-allyloxypyridine, a carboxylic acid, and toluene with methyl triflate. Subsequent warming of the reaction mixture in the presence of potassium carbonate leads to efficient formation of allyl esters in good to excellent yields.

Keywords:

Esterification, Protecting Groups, Oxypyridinium Salt, Nucleophilic Substitution, Allylation

Introduction

2-Benzyloxy-1-methylpyridnium triflate[1,2] (**1**) has been shown to transfer a benzyl group upon warming to nucleophiles including alcohols,[3] carboxylic acids,[4] and electron-rich aromatic rings.[5] Derivatives of oxypyridinium salt **1** have been designed which transfer other fragments including *p*-methoxybenzyl,[6] halobenzyl,[7] and *t*-butyl groups[8] to various nucleophiles. Oxypyridinium salt **1** serves as a pre-activated variant of a trichloroacetimidate, inspired by Mukaiyama's reagent.[9] However, Mukaiyama's reagent activates carboxylic acids for an acyl transfer reaction. On the other hand, compound **1** generates benzyl esters via an "S_N1-like" pathway in which a benzyl cation is formed and trapped with the carboxylic acid, Scheme 1. Triethylamine serves to activate the carboxylic acid.[4] Each of these pathways to benzyl esters proceed without the need for extreme pH. Based on this proposed mechanism, it is reasonable that an analogous allyl pyridyl salt could be designed to transfer allyl groups. This letter focuses on the design and utility of such an allyoxy pyridyl reagent towards the synthesis of allyl esters, which are of particular interest because of their popularity as a protecting group for carboxylic acids.[10] Allyl esters are readily and selectively deprotected under mild conditions with a variety of palladium sources.[11]

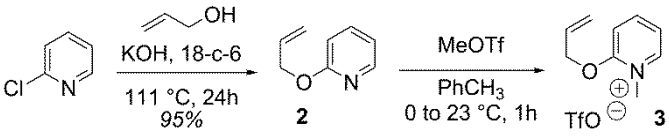


Scheme 1. The conversion of carboxylic acids to esters using 2-benzyloxy-1-methylpyridinum triflate.[4]

Allyl esters have been prepared traditionally by treating a carboxylic acid with an allyl halide under basic conditions.[12] The use of allyl isopropenyl dicarbonate[13] or diallyl dicarbonate[14] with DMAP have also been shown to yield allyl esters. Alternatively, acidic conditions can be used with allyl trichloroacetimidates[15] or allyl alcohols.[16] More modern methods include the Tsuji-Trost reaction using a nucleophilic carboxylic acid with an electrophilic π-allyl Pd species.[17] A variation of this method utilizing secondary homoallylic alcohols was recently reported.[18] More complex substituted allyl esters have been efficiently synthesized by oxidative C-H bond activation.[19]

Results and Discussion

The title compound, 2-allyloxy-1-methylpyridinium triflate (**3**), was initially synthesized according to Scheme 2. Allyl alcohol was combined with 2-chloropyridine, potassium hydroxide, and 18-crown-6 in toluene and was heated at 111 °C to yield 2-allyloxypyridine (**2**) in excellent yield.[20] Compound **2** was efficiently alkylated with MeOTf, however the product, 2-allyloxy-1-methyl-pyridinium triflate (**3**) is an amorphous solid which is difficult to handle, isolate, and store.

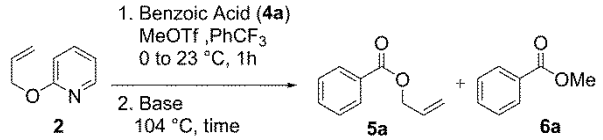


Scheme 2. Synthesis of 2-allyloxypyridinium triflate.

As a result of the physical nature of compound **3**, an alternative idea to generate the oxypyridinum salt *in situ* in the presence of a carboxylic acid substrate was pursued to synthesize allyl esters directly. Initial studies utilized benzoic acid (**4a**) as a substrate to investigate the optimal reaction conditions. In each trial, of MeOTf was added to the reaction mixture at 0 °C. Upon complete consumption of allyloxypyridine (**2**) as monitored by TLC, the reaction was allowed to warm to room temperature, and then allowed to stir at 104 °C in $PhCF_3$ until complete consumption of the carboxylic acid substrate, **4a**. The reaction was quenched after 24h regardless of completion. Initial optimization focused on adding a variety of mild bases to the reaction to activate the carboxylic acid, Table 1.

The *in situ* formation of **3** and immediate reaction with benzoic acid (**4a**) led to the formation of allyl benzoate (**5a**). When no base was added to the reaction mixture, a majority of the starting material remained even after 24h at reflux. Similarly, a variety of weakly basic amines resulted in incomplete consumption of the carboxylic acid, although the reaction did proceed farther as the basicity of the amine increased (Table 1, entries 6-8). It is particularly noteworthy that NEt_3 was proven to be the most effective additive for the benzylation of carboxylic acids with oxypyridinium salt **1**,[4] but was not as effective with allyl derivative **3**. The addition of MgO appeared to slow down the reaction relative to trials with no base additive. Only bicarbonate and carbonate (Table 1, entries 3-5) completely consumed the starting material in less than 24h. Of the two, K_2CO_3 led to a much faster reaction.

Table 1 Initial Base Screening.for *In Situ* Allylic Esterification Reactions.[a]



Entry	Base	Time (h)[b]	Ratio5a:4a[c]	Ratio 5a:6a[d]
1	None	24	1:1	18:1
2	MgO	24	1:3	25:1
3	$NaHCO_3$	8	>99:1	19:1
4	K_2CO_3	1.5	>99:1	22:1
5[e]	K_2CO_3	1	>99:1	20:1
6	Lutidine	24	1:13	>25:1
7	NEt_3	24	3:1	9:1
8	DBU	24	14:1	11:1

[a]Reactions were run with 2.0 equiv. of allyloxypyridine and MeOTf, and 1.0 equiv. of benzoic acid and base.
[b]Reactions were monitored for completion by TLC up to 24h.
[c]The ratio of allyl ester product to remaining starting material was approximated by ^{1}H NMR of the crude reaction mixture after 24h.
[d]The ratio of allyl to methyl ester was approximated by ^{1}H NMR of the crude reaction mixture.
[e]The reaction solvent was switched from $PhCF_3$ to $PhCH_3$ and heated at 111 °C.

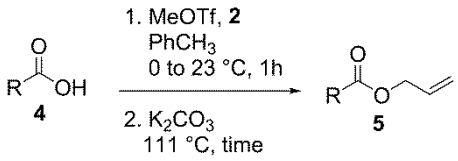
The crude reaction mixture was evaluated by ^{1}H NMR to assess product formation versus remaining starting material and/or byproduct formation. In general, a mixture of the desired allyl ester (**5a**), and the corresponding methyl ester (**6a**) were generated. To identify if the carboxylic acid substrate was directly reacting with MeOTf, several trials were attempted in which the carboxylic was not added until complete consumption of compound **2** occurred. However, no significant difference in the product ratio **5a**:**6a** was observed, so the methyl ester product presumably comes from the carboxylic acid or carboxylate species attacking the pyridinium N-Me group in compound **3**. The methyl ester byproduct was formed even in the absence of base (Table 1, entry 1). In most instances, approximately 4-10% of the product mixture was **6a**. The use of 2,6-lutidine as an additive was the exception, where no sign of the methyl ester was detectable by ^{1}H NMR analysis of the crude reaction mixture (Table 1, entry 6). However, less than 10% of **4a** was consumed after 24h, so the corresponding methyl ester ^{1}H NMR signals may not have resolved from the spectrum baseline. Ultimately, potassium carbonate proved to be the most effective base for the reaction due to its superior efficiency in consuming the starting material, even though some of the methyl ester byproduct was generated as well.

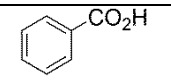
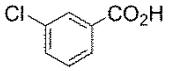
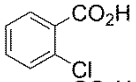
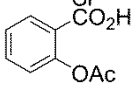
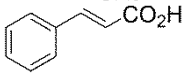
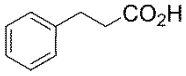
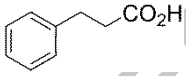
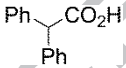
Reactions with **1** typically favor $PhCF_3$ in order to minimize Friedel-Crafts reactions of the resultant benzyl cation with the solvent.[5] However, the allyloxy salt (**3**) seems to be more stable than **1**, and $PhCH_3$ (Table 1, entry 5) was found to be a suitable solvent with no detection of allylarene products. The use of toluene also allowed for a slightly elevated reaction temperature (111 vs. 104 °C), which resulted in faster consumption of the starting material and comparable ratio of the allyl to methyl ester products (Table 1, entry 5 vs. 4).

The fully optimized reaction conditions included combining 1.0 equiv of carboxylic acid with 1.1 equiv of **2** and MeOTf in toluene. After complete formation of **3**, the mixture was heated at reflux and 0.95 equiv of K_2CO_3 was added to the reaction mixture, Table 2. The reaction works well with both aliphatic and aromatic carboxylic acids, typically giving very good to excellent yields of the corresponding allyl ester. The reactions were generally complete with 2h or less of heating. The ^{1}H NMR spectrum of the crude reaction mixture typically indicated that the competing methyl ester (**6**) made up 2-5% of the product mixture. For several of the substrates it was impossible to remove all of **6** by silica gel column

chromatography, but only one example contained more than 1% in the isolated product as indicated by ^{1}H NMR (Table 2, entry b). The reaction proceeds much faster than the corresponding reaction of carboxylic acids with compound **1**,[7] although a stronger base is utilized in this reaction (K_2CO_3 vs. NEt_3). Perhaps this is due to a change in mechanism, where the carboxylate is more directly involved in the rate determining step of the substitution via an S_N2 or S_N2'-like pathway. This potential change in mechanism could also help explain the formation of **6** as a byproduct in this reaction. If oxypyridinium salt **3** does not decompose as readily as **1**, then the carboxylate could directly attack the pyridinium N-Me *via* an S_N2 attack, ejecting allyloxypyridine (**2**) as a leaving group. In fact, the ^{1}H NMR spectrum of the crude reaction mixtures did occasionally shown trace amounts of **2**, even though TLC analysis had shown it to be completely consumed in step 1.

Table 2 Optimized Formation of Allyl Esters Using **3**.[21]



Entry	Carboxylic Acid	Time (h)	Ratio5:6[a]	% Yield[b]
a		1	>99:1	81
b		0.5	33:1	94
c		1.5	99:1	86
d[c]		2	>99:1	71
e		2	>99:1	90
f		1	99:1	91
g		2	>99:1	98
h		1	>99:1	90

[a]The ratio of allyl ester to methyl ester was approximated by ^{1}H NMR of the purified product mixture.
[b]Isolated yields of allyl ester and methyl ester product mixture after column chromatography.
[c]The carboxylic acid substrate was added to the reaction mixture after **3** was completely formed.

Conclusion

In summary, this letter reports a new method for the facile synthesis of allyl esters from a variety of carboxylic acids. This reaction depends upon the formation of 2-allyloxy-1-methylpyridinium triflate (**3**) *in situ*, which in turn serves as an electrophilic allyl source for trapping with a carboxylic acid. This new method should complement other allylation procedures, and offers several advantages including short reaction times and generally high yields. While this work represents an extension of 2-benzyloxy-1-methylpyridnium triflate (**1**), these reactions may proceed through a different

substitution mechanism. A study of the mechanism of this reaction is underway and will be communicated in a later publication.

Acknowledgment

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1. (a) 2-Benzyloxy-1-methylpyridinium triflate [26189-59-3] is licensed, manufactured, and distributed non-exclusively by Sigma–Aldrich Chemical Co., catalog #679674; see: Dudley, G. B. Compounds and methods of arylmethylation (benzylation) as protection for alcohol groups. U.S. Patent Appl. 11/399,300, 2006; (b) ChemFiles **2007**, 7.
2. Albiniak, P. A.; Dudley, G. B. *Synlett* **2010**, 841.
3. (a) Poon, K. W. C.; House, S. E.; Dudley, G. B. *Synlett*, **2005**, 3142. (b) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923. (c) Poon, K. W. C.; Albiniak, P. A.; Dudley, G. B. *Org. Synth.* **2007**, *84*, 295.
4. Tummatorn, J.; Albiniak, P. A.; Dudley, G. B. *J. Org. Chem.* **2007**, *72*, 8962.
5. Albiniak, P. A.; Dudley, G. B. *Tetrahedron Lett.* **2007**, *48*, 8097.
6. Nwoye, E. O.; Dudley, G. B. *Chem. Commun.* **2007**, 1436.
7. Albiniak, P. A.; Amisial, S. M.; Dudley, G. B.; Hernandez, J.P.; House, S. E.; Matthews, M. E.; Nwoye, E. O.; Reilly, M.K.; Tlais, S. F. *Synth. Commun.* **2008**, *38*, 656.
8. Salvati, A. E., Hubley, C. T.; Albiniak, P. A. *Tetrahedron Lett.* **2014**, *55*, 7133.
9. Mukaiyama, T. Angew. Chem. Int. Ed. Engl. **1979**, 18, 707.
10. Guibé, F. *Tetrahedron* **1998**, *55*, 2967.
11. Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 4th ed.; Joh Wiley & Sons, Inc.; New York, **1999**; p591.
12. (a) Friedeich-Bochnitschek, S.; Waldmann, H.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 751. (b) Kunz, N.; Waldmann, H.; Unverzagt, C. *Int. J. Pept. Protein Res.* **1985**, *26*, 493.
13. Takeda, A.; Akiyama, A.; Konda, Y.; Takayanagi, H.; Hariyaga, Y. *Tetrahedron Lett.* **1995**, *36*, 113.
14. Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.-i., Mizuno, Y.; Takayamagi, H.; Hariyage, Y. *Synthesis* **1994**, 1063.
15. Kokotos, G.; Chiou, A. *Synthesis* **1997**, 168.
16. Waldmann, H.; Kunz, H. *Liebigs Ann. Chem.* **1983**, 1712.
17. (a) Trost, B. M.; Crawley, M. L. *Chem. Reviews* **2003**, *103*, 2921. (b) Tsuji, J. *Transition Metal Reagents and Catalysts*; John Wiley & Sons, Ltd.: Chichester, U. K., **2003**; p109.
18. Wang, Y.; Kang, Q. *Org. Lett.* **2015**, *16*, 4190.
19. (a) Vermeulen, N. A.; Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 11323. (b) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.
20. *Procedure for the synthesis of* **2**. A 3-necked, 500 mL, round-bottomed flask was equipped with stir bar, reflux condenser fitted with a N_2 inlet adapter, and 2 glass stoppers. Allyl alcohol (5.80 mL, 88.1 mmol), followed by 2-chloropyridine (5.00 mL, 52.7 mmol), and toluene (105 ml) were added sequentially to the flask. Potassium hydroxide (85%, 12.0g, 176 mmol) was ground in a mortar in pestle, then added to the reaction flask followed by 18-crown-6 (0.278 g, 1.04 mmol). The reaction mixture was heated at reflux (oil bath at 115 °C) for 2h. After cooling to room temperature, the reaction mixture was diluted with diethyl ether (150 mL), washed with water (1 x 50 mL), followed by brine (1 x 50 mL). The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to a pale yellow liquid. Column chromatography of the residue (29:1 hexanes/ethyl acetate) yielded the product as a pale yellow oil (6.73 g, 49.8 mmol, 95%).
21. *General procedure for the formation of allyl esters:* A 5-mL reaction vial was equipped with a stir bar, a rubber septum, and an argon inlet needle. The vial was charged with allyloxypyridine (**2**) (1.1 equiv), carboxylic acid (**4**) (1.0 equiv), and dry $PhCH_3$ (2.5 mL), and was allowed to stir at 0 °C. MeOTf (1.1 equiv) was added dropwise to the reaction mixture over 2 min. Upon complete addition, the ice bath was removed and the reaction was allowed to stir for 1h or until **2** was completely consumed as indicated by TLC. The septum was quickly replaced with a reflux condenser fitted with an N_2 inlet adapter. The reaction mixture was heated at reflux (oil bath 115 °C), and K_2CO_3 (0.95 equiv) was added in one portion through the top of the reflux condenser. Upon complete consumption of the carboxylic acid as indicated by TLC typically (1-2h), the mixture was diluted with ethyl acetate (10 mL). The diluted reaction mixture was washed with water (1 x 10 mL), followed by brine (1 x 10 mL). The organic fraction was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to isolate the crude product mixture. The crude mixture was purified by flash chromatography to yield the allyl ester product (**5**).

Graphical Abstract