Pergamon

Tetrahedron Letters 40 (1999) 2685–2688

TETRAHEDRON LETTERS

Picolinic Acid as a Partner in the Mitsunobu Reaction: Subsequent Hydrolysis of Picolinate Esters under Essentially Neutral Conditions with Copper Acetate in Methanol

Tarek Sammakia* and Jon S. Jacobs

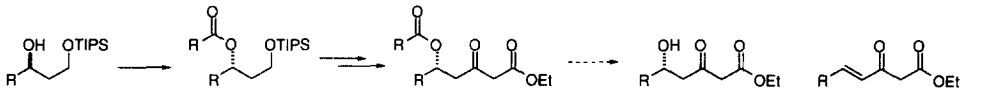
Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309-0215

Received 15 December 1998; revised 5 February 1999; accepted 8 February 1999

Abstract: The use of picolinic acid and 6-methyl picolinic acid in the Mitsunobu reaction has been studied. These substrates are excellent partners in the Mitsunobu reaction, and offer the added advantage that the resulting esters can be cleaved under essentially neutral conditions using $Cu(OAc)_2$ and methanol.

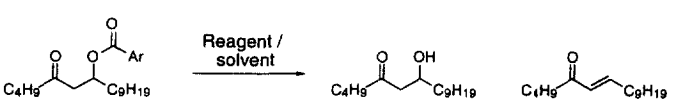
Keywords: Mitsunobu reaction; inversion reactions; hydrolysis; copper

Since its inception in 1967, the Mitsunobu reaction has served as a useful method for the inversion of hydroxyl bearing stereocenters.[1] Recent advances in understanding the mechanism of this reaction[2] have led to the use of carboxylic acids more acidic than benzoic acid, such as *para*-nitrobenzoic acid[3] and chloroacetic acid,[4] as partners and low temperatures in the formation of the activated phosphorane.[5] These modifications have extended the utility of this method to hindered substrates that were not amenable to the original procedure. However, there are still substrates for which the application of the Mitsunobu reaction sequence can be problematic. We encountered one such substrate during the course of a total synthesis wherein we needed to invert a hydroxyl stereocenter which later in the synthesis became β- to a carbonyl group (Scheme 1). The most obvious solution to this problem involved first inverting the hydroxyl group using the Mitsunobu reaction, and carrying the Mitsunobu product through the homologation sequence



Scheme 1 **1** **2** **3**

before hydrolyzing the ester to reveal the desired β-hydroxy ketone. However, this sequence suffers from the potential of elimination of the β-acyloxy group of **1** to generate the conjugated enone **3** during the hydrolysis of the ester (Scheme 1), and we wished to study this transformation on a simple model. We therefore prepared substrates **4** and **5** (Scheme 2), and examined a variety of conditions for their conversion to the corresponding β-hydroxy ketone (**6**). Alkaline conditions, including hydroxide ion in various solvents as well as milder reagent combinations such as K_2CO_3 / MeOH or $Mg(OMe)_2$ / MeOH,[6] provided elimination as the predominant product, and less than 10% of **6**. Distannoxane catalyzed transesterification did provide **6** as the major product, however the reaction was prohibitively slow; after 6 days using 0.3 equiv $(Bu_2ClSn)_2O$ in refluxing chloroform / methanol or refluxing toluene / methanol, only 30% conversion was observed. In this communication, we describe a solution to this problem which involves the use of picolinic acid as a



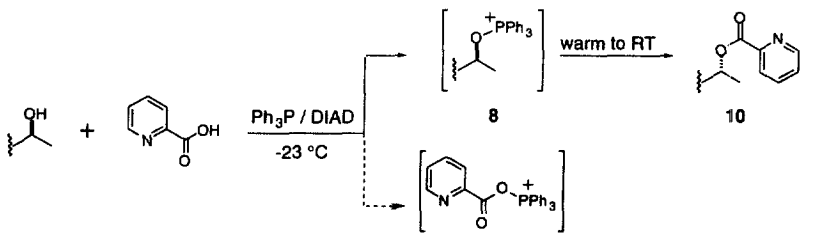
Scheme 2 **4**, Ar = Ph; **5**, Ar = 4-NO_2Ph, **6** (minor) **7** (major)

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00332-9

partner in the Mitsunobu reaction, and subsequent hydrolysis of the resulting esters under essentially neutral conditions with $Cu(OAc)_2$ in chloroform / methanol solutions.[7]

Picolinic acid as a partner in the Mitsunobu reaction: We have examined the efficacy of picolinic acid as a partner in the Mitsunobu reaction using Coleman's conditions[5] in which the reaction is initially conducted at -23°C, then warmed to room temperature. This procedure ostensibly allows for the formation of the oxyphosphonium salt (**8**) of the alcohol at low temperature, and disfavors the formation of the acyloxy-phosphonium salt **9** (Scheme 3). The formation of **9** is non-productive, and can lead to acylation of the alcohol with retention of configuration. Upon warming the solution, the activated oxyphosphonium salt can undergo attack by the carboxylate in an S_N2 fashion to provide the inverted ester **10**. We chose substrates bearing a range of steric and electronic demands to examine this reaction, and in some instances, compared our results with those obtained using *para*-nitrobenzoic acid as a partner (Table 1). We find that picolinic acid is an excellent substrate for the Mitsunobu reaction, and that these conditions consistently provide high yields in the reaction even with hindered substrates such as menthol or 1-phenyl-2-methylpropanol (entries 1, 4, 9, and 12, Table 1). The reaction proceeds with >98% inversion (no detectable retention by ^1H NMR) in the cases of entries 1, 4, 10 and 12 in Table 1, and with 3% retention in the cases of entries 9 and 12 in Table 1. The stoichiometry of the reaction is important, with less than 4 equivalents of reagents providing incomplete conversion (compare entries 1-3, Table 1). 6-Methyl picolinic acid is also an effective partner in the reaction, and provides high yields even with the more hindered substrates (entries 4 and 11-13, Table 1).

Typical experimental procedure for the Mitsunobu reaction: A 25 mL round bottom flask was charged with picolinic acid (312 mg, 2.53 mmol), menthol (99 mg, 0.634 mmol), and triphenylphosphine (664 mg, 2.53 mmol). The flask was flushed with nitrogen, and THF (7 mL, freshly distilled from Na) was added, and the solution cooled to -20°C (20% aqueous $CaCl_2/CO_2$ bath) for 10-15 min. Diisopropyl azodicarboxylate (DIAD, 499 µL, 2.53 mmol) was then added dropwise to the solution over 3 min. The temperature of the bath was maintained at -20 to -25°C for 4.5 h, and the cold bath allowed to slowly warm to ambient temperature and allowed to stir overnight. The reaction mixture was then concentrated at reduced pressure, and the products were purified by flash chromatography (the crude mixture was applied to the column using a minimal amount of CH_2Cl_2 and eluted with hexanes then 5:1 hexanes / ethyl acetate) to provide the picolinate ester of neomenthol (132 mg, 0.505 mmol, 80%).



Scheme 3

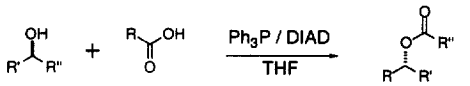
Copper promoted methanolysis of picolinate esters: With the success of the Mitsunobu reaction in hand, we then examined the lability of picolinate esters towards copper acetate promoted methanolysis.[7] The picolinate esters shown in Table 2 were treated with varying amounts of copper acetate in methanol or methanol / chloroform mixtures at room temperature. For typical substrates, we found that sub-stoichimoetric amounts of copper were sufficient; however, with the more hindered substrates, stoichiometric amounts of copper were required for practical reaction times. 6-Methyl-picolinate esters were found to be less reactive under these conditions, probably due to weaker binding to the copper, while *para*-nitrobenzoate esters, which do not contain a metal binding site, showed no methanolysis after 5 days. *Most notably, picolinate esters of β-hydroxy ketones underwent smooth methanolysis with no evidence of elimination.*

Typical experimental procedure for the methanolysis of picolinate esters: A 10 mL round bottom flask was charged with $CHCl_3$ (3 mL), ester **11** (Table 2, entry 3, 91 mg, 0.253 mmol), methanol (89

μL, 2.08 mmol) and $Cu(OAc)_2$ (23 mg, 0.126 mmol). The reaction was allowed to stir for 6 h at which point it was judged complete by TLC. The reaction was diluted with hexanes (1 ml) and washed with disodium EDTA (1ml of a 0.1 M solution). The organic layer was dried ($MgSO_4$), filtered, and concentrated to an oil. Flash chromatography (hexanes then 5:1 hexanes / ethylacetate) provided the corresponding β-hydroxyketone (55 mg, 0.223 mmol, 85%).

In conclusion, we have found that picolinic acid is an excellent partner for the Mitsunobu reaction, and that the methanolysis of picolinate esters with copper acetate in methanol proceeds smoothly under essentially neutral conditions. This mild protocol should be useful for performing this transformation in molecules which contain base sensitive functionality.

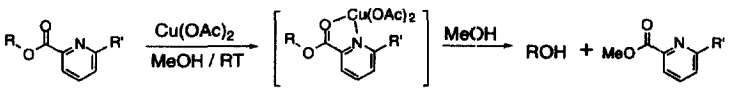
Table 1. Picolinic acid as a partner in the Mitsunobu reaction

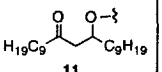
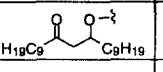
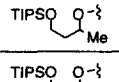
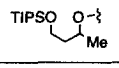
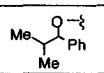
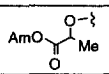
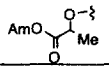


entry	Alcohol	RCO_2H (equiv)	Equiv PPh_3	Equiv DIAD	Temp (Time)	Yield
1		 (4)	4	4	-20 °C (3h), then RT (16h)	80 %
2	" "	" " (3)	3	3	" "	70 %
3	" "	" " (2)	2	2	" "	67 %
4	" "	 (4)	4	4	" "	81 %
5	" "	 (4)	4	4	" "	83 %
6	" "	 (4)	4	4	0 °C (5 min), then R.T. (14 h), then 40 °C (3h)[a]	88 %
7	" "	 (4)	4	4	0 °C (5 min), then R.T. (14 h)	62 %
8		 (4)	4	4	-20 (3h), then RT (16h)	79 %
9		" " (4)	4	4	" "	94 %
10		" " (4)	4	4	" "	89 %
11		 (4)	4	4	" "	89 %
12		" " (4)	4	4	" "	85 %
13		" " (4)	4	4	" "	95 %

a) Reaction was conducted according to the procedure in reference 3b.

Table 2. Copper acetate promoted methanolysis of picolinate esters.



entry	RO–	R'	Equiv $Cu(OAc)_2$	Time	Yield
1		H	1	2 d	79 %
2		Me	10	5 d	86 %
3	 11	H	0.5	6 h	85 %
4		Me	0.5	3 d	82 %
5		H	2	2 h	91 %
6		Me	5	10 h	90 %
7		H	2	24 h	95 %
8		Me	2	5 d	88 %
9		H	2	6 h	72 %
10		Me	2	18 h	90 %

Acknowledgment. We thank the National Institutes of Health (GM 48498) and Novartis for financial support of this research. T.S. is a recipient of an American Cancer Society Junior Faculty Research Award and is an Alfred P. Sloan Research Fellow.

1 Reviews: Mitsunobu, O. *Synthesis* **1981**, 1; Hughes, D. L. *Org. Prep. and Proc. Int.* **1996**, *28*, 127; Hughes, D. L. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1992; Chapter 2.

2 Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235; Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487; Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045; Macor, J. E.; Wehner, J. *Heterocycles* **1993**, *35*, 349; Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967.

3 a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017; b) Dodge, J.A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234; c) Dodge, J. A.; Nissen, J. S.; Presnell, M. *Org. Synth* **1996**, *73*, 110.

4 Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317

5 Coleman, R. S.; Grant, E. B. *Tetrahedron Lett.* **1994**, *35*, 8314.

6 Xu, Y-C.; Bizauneh, A.; Walker, C. *J. Org. Chem.* **1996**, *61*, 9086

7 For examples of copper-promoted hydrolysis reactions, see: Kroll, H. *J. Am. Chem. Soc.* **1952**, *74*, 2036; Bender, M. L.; Turnquist, B. W. *J. Am. Chem. Soc.* **1957**, *79*, 1889; Corey, E.J.; Dawson, R. L. *J. Am. Chem. Soc.* **1962**, *84*, 4899; Agren, A. *Acta Pharm. Suecico* **1965**, *2*, 87; Hay, R. W; Basak, A. K. *J. Chem. Soc. Dalton Trans.* **1986**, 39.