Pergamon

Tetrahedron Letters 40 (1999) 5601–5604

TETRAHEDRON LETTERS

1,2,3,4-Tetrahydro-1-naphthyl ester as a selective protecting group for carboxylic acids

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Received 12 January 1999; revised 18 May 1999; accepted 25 May 1999

Abstract

The carboxylic acid functionality can be protected as the 1,2,3,4-tetrahydro-1-naphthyl ester, which can be selectively cleaved in the presence of aryl and alkyl esters using chlorotrimethylsilane and sodium iodide in acetonitrile. This protecting group allows room temperature deprotection under essentially neutral conditions throughout the cleavage reaction. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: cleavage reaction; chlorotrimethylsilane; sodium iodide; esters

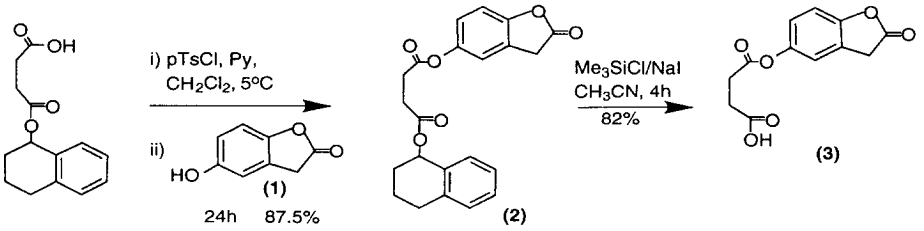
The synthesis of complex molecules has required the organic chemist to develop increasingly subtle protecting groups together with effective methods for their formation and removal. Esters have long been the intermediates of choice for the protection of alcohols or carboxylic acids. Deprotection of carboxylic acids was initially achieved under somewhat severe basic or acidic conditions, warranting the development of a number of selective protecting groups capable of regenerating carboxylic acids under milder conditions, ie. hydrogenolysis of benzyl esters. The discovery, concurrently by Ho and Olah [1] and by Jung and Lyster [2], that esters could be cleaved by iodotrimethylsilane provided another alternative route to carboxylic acid deprotection although this may not be considered a particularly mild reagent. It was later shown that iodotrimethylsilane could be replaced by the more convenient, although somewhat slower, use of equimolar amounts of chlorotrimethylsilane and sodium iodide which also reduced the potential exposure of the ester to HI [3,4]. A review of the reactions of the halotrimethylsilanes has been published by Schmidt [5].

The inability of iodotrimethylsilane or its equivalent to cleave aryl esters makes it an ideal reagent for the selective removal of alkyl groups from mixed alkyl, aryl diesters. However the initial communication suggested little selectivity between alkyl groups under the high temperatures used in the reaction[1] and subsequent publications differ in the order of selectivity at lower temperatures[6,7]. In this letter we report that the ester

PII: S0040-4039(99)01040-0

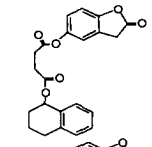
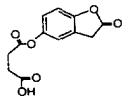
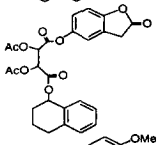
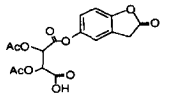
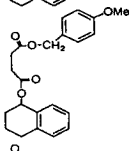
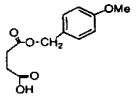
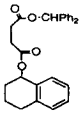
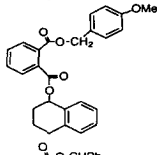
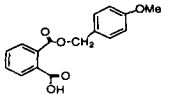
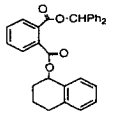
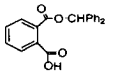
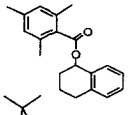
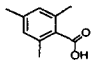
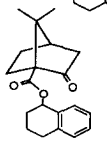
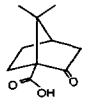
formed from 1,2,3,4-tetrahydro-1-naphthol can be preferentially cleaved by chlorotrimethylsilane/sodium iodide in acetonitrile at room temperature in the presence of other alkyl and aryl esters. The use of acetonitrile as solvent was found to be critical as no preference was observed when the reaction was performed in dichloromethane. This may be related to the proposed complex formed between trimethylsilyl halides and acetonitrile [4]. This procedure was used in the indirect synthesis of 2,5-dihydroxyphenylacetic γ-lactone-5-hydrogen succinate (**3**) scheme 1, a hapten applicable for the generation of antibodies against the mycotoxin patulin. The direct synthesis of this compound from succinic anhydride and 2,5-dihydroxyphenylacetic γ-lactone (**1**) had proved difficult due to the formation of numerous by-products.

Scheme 1



The applicability of 1,2,3,4-tetrahydro-1-naphthyl as a protecting group was investigated by the synthesis and then cleavage of a series of esters, table 1. Entries 1-6 were synthesised [8] as shown in scheme 1, with the appropriate alcohol in place of (**1**). Entries 5 and 6 were also prepared by coupling 1,2,3,4-tetrahydro-1-naphthol to the corresponding hemiphthalate using DCC [9], BOP-Cl [10] or a mixed anhydride method. Similarly the 1,2,3,4-tetrahydro-1-naphthyl ester of 2,4,6 trimethylbenzoic acid (entry 7) could be made in isolated yield of 45%(DCC) and 52%(BOP-Cl); the low yields are probably due to steric hindrance. The corresponding ester of (*1S*)-(+)-ketopinic acid (entry 8) was similarly produced with the following yields: 70%(DCC) and 80%(BOP-Cl). The mixed anhydride method, with these two acids, produced no relevant product, probably because of steric effects. When the standard reaction conditions [11] are applied to these compounds cleavage of the 1,2,3,4-tetrahydro-1-naphthyl group is observed (table 1). No cleavage of methyl, isopropyl or phenyl groups was observed under these conditions (data not shown) and the 1,2,3,4-tetrahydro-1-naphthyl group is cleaved in preference to both the benzhydryl and *p*-methoxybenzyl groups that have previously been cleaved with this reagent [7].

Table 1

entry	substrate	product	reaction time (h)	% yield *
1			4.0	82
2			4.0	78
3			1.5	70
4			1.5	65
5			2.0	65
6			2.0	60
7			1.0	80
8			1.0	75

* yield calculated from product isolated by column chromatography and confirmed by nmr

Treatment of entries 5 and 6 with trifluoroacetic acid, in dichloromethane at rt for 1h [12], resulted in the total cleavage of all the ester groups. This result suggests that the reported instability of the *p*-methoxybenzyl group to iodotrimethylsilane may result from HI in the reaction mixture. Similarly, hydrogenolysis [13] of entries 5 and 6 over 10% Pd/C resulted in the total cleavage of the ester groups. However both entries 5 and 6 were stable

to CAN [14] in aqueous acetonitrile, for 4h at 0°C and to treatment with DDQ [14] in aqueous dichloromethane for 18h; total recovery of starting material, after column chromatography, being obtained. The 1,2,3,4-tetrahydro-1-naphthyl group was also shown to be stable to sodium borohydride reduction (MeOH/0°C) and acetylation (Ac_2O/py/rt).

These results suggest that the 1,2,3,4-tetrahydro-1-naphthyl ester is a very useful protecting group for carboxylic acids. It can be cleaved in preference to other esters by using chlorotrimethylsilane/sodium iodide in acetonitrile at room temperature. Its value in synthetic chemistry is enhanced by its synthesis using a number of different coupling procedures, its demonstrated stability to reagents such as DDQ and CAN under cleavage conditions, and its stability to borohydride and acetylation.

Acknowledgements We are grateful to the Ministry of Agriculture, Fisheries and Food for financial support for this work which forms part of the FS2061 programme of study.

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[11] The appropriate mixed di-ester (5mmole) in acetonitrile(10ml), together with chlorotrimethylsilane (1 equivalent) and sodium iodide (1 equivalent) was stirred at room temperature. Analysis samples (0.5ml) were removed and diluted with H_2O (0.2ml). On completion the reaction mixture was diluted with water (5ml) and then extracted with ethyl acetate (2x10ml). The organic fraction was then washed with 0.1M sodium thiosulphate solution (2x15ml) followed by 0.5M sodium chloride solution (15ml). After the removal of solvent, the dried carboxylic acid was purified by flash chromatography using 20% ethyl acetate in hexane. All isolated products gave satisfactory analysis as typified by **3**. Crystallisation from acetone/hexane gave **3** (82% yield) mp. 114-116°C; υ_{max} 1784.0, 1753.4 & 1735.6; δ(*d*-DMSO)7.0-7.4(3H, m), 4.0(2H, s), 2.85(2H, t, J=6.6Hz), 2.6(2H, t, J=6.6Hz). (Found C, 57.6; H, 4.1 $C_{12}H_{10}O_6$ requires C, 57.6; H, 4.0%).

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