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Cyclopentyl: A Novel Protective Group for Phenols

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Abstract: We have discovered cyclopentyl as a novel group for the protection of hydroxyl functionality of phenols. The key steps involved are cyclopentylation and decyclopentylation.

Keywords: alkyl aryl ether, phenol, protective group

INTRODUCTION

The selective protection and removal of protecting groups is of critical importance in many synthetic sequences. A protecting group should be easy to introduce, easy to cleave, and stable during the course of various reaction conditions. Protection of the hydroxyl functionality of phenols is required to prepare a number of compounds.[1–5] There are various protecting groups reported in the literature for the protection of hydroxyl functionality of phenols such as methyl, methoxymethyl (MOM), methoxyethoxymethyl (MEM), methylthiomethyl (MTM), benzyloxymethyl (BOM), tetrahydropyranyl (THP), ethoxy-ethyl (EE), benzyl (R-OBn), 2-napthylmethyl (NAP), *p*-methoxybenzyl (PMB), *o*-nitrobenzyl, *p*-nitrobenzyl, 9-phenylxanthyl (pixyl, px), trityl -CPh_3 (Tr), triisopropylsilyl (iPr3Si, TIPS), phenyldimethylsilyl, *t*-butyldimethylsilyl (t-BuMe2Si- or TBDMS), *t*-butyldiphenylsilyl (t-$BuPh_2Si$-), and esters such as acetates, trifluoroacetate, pivaloate, and

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benzoate.[6] A protecting group should be easy to introduce, easy to cleave, and stable under various reaction conditions.

The new chemical entities required for our drug discovery program were synthesized by multistep synthetic methods.[7] During the course of this work, a suitable protecting group was required for some of our phenolic intermediates. For our purpose, an alkyl/cycloalkyl protecting group was considered to be the most suitable one. Initially, we used methyl as a protective group, but its removal at the desired stage required very harsh conditions such as refluxing over a long period using HBr/acetic acid or BBr_3 or $AlCl_3$ or alkyl/aryl thiolate. We also tried isopropyl as a protective group but it turned out to be less stable under some of our reaction conditions. The idea of using cyclopentyl as a protective group came from the observations that some of our cyclopentyloxy aryl intermediates underwent decyclopentylation to some extent under Lewis acid (using stannous chloride). We confirmed this by trying several Lewis acid conditions for removal and found that 33% HBr in acetic acid or 48% aq. HBr can cleave this group readily. Although there are some compounds reported in the literature as having a cyclopentyloxy aryl moiety,[8] but practically there are no reports on cyclopentyl as a protective group for phenols. We now report cyclopentyl as a novel protective group for phenols.

We prepared several new chemical entities using cylopentyl as a protective group. We found that cyclopentyl is stable under various reaction conditions such as bromination, oxidation, and acid chloride preparation. It is also easily cleavable with commercially available 48% aqueous hydrobromic acid or 33% hydrobromic acid in acetic acid.

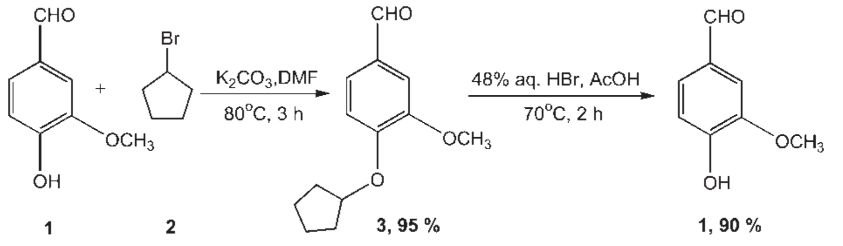
RESULTS AND DISCUSSION

4-(Cyclopentyloxy)-3-methoxy benzaldehyde **3** was prepared by reaction of vanillin **1** and cyclopentyl bromide **2** in the presence of potassium carbonate using N,N-dimethyl formamide as solvent with a yield of 95%.

Decyclopentylation of **3** using 48% aqueous HBr in acetic acid resulted in vanillin **1**. Also, decyclopentylation is preferred over demethylation under the given conditions.

EXPERIMENTAL

Commercial solvents and reagents were used without further purification. ^{1}H NMR spectra were recorded on a Varian 300-MHz spectrometer. Melting points are uncorrected. Elemental analysis was performed on a Perkin-Elmer analyzer. Mass spectra were recorded on Thermo Finnigan LCQ DECA XP MAX (Ion Trap) mass spectrometer using an APCI (atmospheric pressure chemical ionization) source in positive mode at capillary voltage 3.14 V and capillary temperature 250°C (Scheme 1).



Scheme 1.

4-(Cyclopentyloxy)-3-methoxy Benzaldehyde 3

To a well-stirred solution of vanillin **1** (10 g, 0.0657 mol) and anhydrous potassium carbonate (18.15 g, 0.1315 mol) in N,N-dimethyl formamide (70 mL), cyclopentyl bromide **2** (10.78 g, 0.0723 mol) was added and heated to 80°C for 3.0 h. Consumption of starting material was checked by means of thin-layer chromatography (TLC). The reaction mixture was then cooled to room temperature and filtered to remove inorganic material. The filtrate was then concentrated under reduced pressure. The residue obtained was diluted with 5% aqueous hydrochloric acid solution (100 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave **3** as light yellow oil with a yield of 13.8 g (95%). IR (KBr): 2961, 1682, 1594, 1583, 1424, 1266, 1135, 1032, 980 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.63–2.03 (8H, m), 3.89 (3H, s), 4.86 (1H, quint.), 6.96 (1H, d, $J = 8.1$ Hz,), 7.39 (1H, s), 7.42 (1H, d, $J = 8.1$ Hz), 9.82 (1H, s). Anal. calcd. for $C_{14}H_{18}O_2$: C, 77.11, H, 8.36. Found: C, 77.16; H, 8.45. MS: 221 $[M + H]^+$.

Vanillin 1

A solution of 4-(cyclopentyloxy)-3-methoxy benzaldehyde **3** (10 g, 0.0452 mol) and 48% aqueous HBr (25 mL) in glacial acetic acid (500 ml) was stirred at 70°C for 2 h. The progress of the reaction was monitored by TLC. Finally, the reaction mixture was concentrated under reduced pressure and diluted with ice water (100 L). The solid was filtered and washed with ice water (4 × 25 mL) and petroleum ether (2 × 25 mL) and dried to afford vanillin **1** as a light yellow solid with a yield of 4.9 g (71%), mp 79–81°C. IR (KBr): 3192, 1693, 1604, 1312, 1248, 1193, 1087, 1052, 926, 842, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.96 (1H, s), 6.30 (1H, s), 7.05 (1H, d, $J = 8.4$ Hz), 7.41 (2H, brs), 0.82 (1H, s). Anal. calcd. for $C_8H_8O_3$: C, 63.21, H, 5.35. Found: C, 63.17; H, 5.29.

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