SHORT PAPER

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Efficient and low cost synthesis of the 2-(*tert*-butyldiphenylsilyloxymethyl)benzoyl chloride for the protection of nucleobases†

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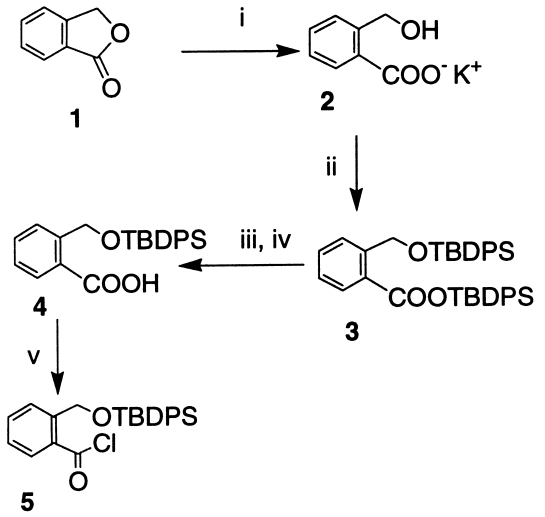
The title compound was easily obtained starting from cheap phthalide in four steps with an overall yield of 67%.

Keywords: protecting group, phthalide, fluor labile

The synthesis of base-sensitive oligonucleotides or base-sensitive conjugate-oligonucleotides requires the use of exocyclic amino protecting groups that are removed under mild (tert-butylphenoxyacetyl[1], PNT[2], AMB[3]) or neutral (allyloxy[4], diNPEOC[5]) conditions. Among the different protecting groups reported in the literature for that purpose, the 2-(*tert*-butyldiphenylsilyloxymethyl)benzoyl (SiOMB) group was introduced in early 1990s by the group of van Boom. Using the SiOMB protection, they synthesised a short nucleopeptide and RNA[6,7]. The SiOMB can be removed rapidly with fluoride ion (*e.g.* dry TBAF in THF). After hydrolysis of the TBDPS group, the remaining (ortho-methyloxy)benzoyl group is spontaneously removed by an intramolecular attack of the hydroxyl on the carbonyl to form the phthalide and the unprotected nucleobase. In the original paper[7] the SiOMB chloride was prepared in four steps from 2-bromobenzylalcohol using a Grignard reaction with an overall yield of 63%. As the starting compound 2-bromo-benzylalcohol is quite expensive (≈250 €/mol) we looked for a synthesis of SiOMB chloride with a cheaper starting material. Thus we developed a synthesis starting from phthalide **1** (≈16 €/mole) that yielded the SiOMB chloride **5** in four steps with an overall yield of 67% (Scheme 1).



Scheme 1
i: KOH, 85 % methanol aq.; ii: TBDPSCl dry pyridine; iii: K_2CO_3, H_2O, THF methanol; iv: 1 M $KHSO_4$ to pH 4-5; v: oxalyl chloride, dry toluene.

The phthalide **1** was opened by treatment with a 85% methanol aqueous solution of potassium hydroxide under reflux for 1h 30[8] to give the compound **2**. After evaporation the residue was directly dissolved in pyridine and silylated overnight with 2.2 eq of *tert*-butyldiphenylsilyl chloride to give the bis silylated compound **3** which could be eventualy crystallised from methanol or used directly for the next step. A selective hydrolysis of the carboxylic function with aqueous potassium carbonate in methanol and THF for 30 min followed by acidification to pH 4-5 with potassium hydrogen sulfate yielded the expected compound **4**. The purification was achieved by crystallisation from hexane. The pure compound can be stored for a long time. It was quantitatively converted into its chloride **5** by treatment with oxalyl chloride in toluene at 50°C for 1 h, just prior to its use for the protection of the nucleobases of nucleoside according to the transient protection of hydroxyl functions with trimethylsilyl groups[9].

By this method, the compound **4** was rapidly obtained, without any intermediate purification and it was easily purified by a simple crystallisation from hexane. Its quantitative convertion with oxalyl chloride[7] gave the title compound **5** with an overall yield of 67%. This reaction was performed on a scale using up to 10 g of the starting material.

Experimental

A solution of phthalide (268 mg, 2 mmol) and KOH (112 mg, 2 mmol) in 85% methanol aqueous (2 ml) was refluxed for 1h30, after evaporation the residue was dissolved in dry pyridine (5 ml) and TBDPS chloride (1.13 ml, 4.4 mmol) was added and stirred overnight at room temperature. The mixture was treated with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. After evaporation the crude residue was dissolved in methanol (20 ml) and THF (7 ml) and treated with an aqueous solution of K_2CO_3 (700 mg, 7 ml). After 30 min, the solution was concentrated in vacuum to one-quarter volume and diluted with brine (20 ml). The resulting mixture was cooled to 0°C adjusted to pH 4–5 with 1N aqueous potassium hydrogen sulfate solution), extracted with diethyl ether (2x50ml) and dried over sodium sulfate. After evaporation the compound **4** was crystallised from hexane (521 mg, 67%).

For **4**: ^{1}H NMR ($CDCl_3$ + CD_3OD) δ (ppm) : 7.89–7.20 (m, 14H, H Ar); 5.12 (s, 2H, CH_2); 1.08 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ (ppm) : 176.08 (C=O,COOH), 140.26 ($\underline{C}CH_2$), 133.99 (CSi, phenyl), 126.27–136.04 (CH Ar), 125.84 (*C*C=O), 64.36 (CH_2), 27.03 (C($\underline{C}H_3)_3$), 19.60 ($\underline{C}(CH_3)_3$); HR-FAB (positive mode) calc. for $C_{24}H_{27}O_3Si$ 391.1729, found 391.1726.

A solution of **4** (858mg, 2.2 mmol) and oxalyl chloride (481µl 5.5 mmol) in dry toluene was heated 1h at 50 °C. After evaporation the resulting compound **5** was quantitatively obtained and used directely as a 0.5 M solution in dioxane.

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