JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo300598d • Publication Date (Web): 18 Jul 2012

A method for activation and recycling of trityl resins

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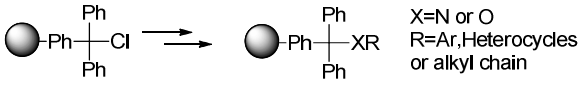

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Abstract

This note describes a rapid and mild strategy for the loading of alcohols and anilines onto a polystyrene triphenylmethyl (trityl) resin. High loadings were obtained in a matter of minutes by treating resin bound trityl chloride with triethyloxonium tetrafluoroborate followed by alcohols or anilines. Yields were comparable or better than known literature methods. Recycling of the recovered resin was also possible using the developed method.

Keywords: Solid-Phase, Trityl resin, Activation, Recycling

The development of combinatorial chemistry has been accompanied by a huge interest in solid-phase organic synthesis. A crucial feature of solid-phase synthesis is the attachment of the substrate to the polymeric support.[1] The first building block has to be attached efficiently, the linkage has to be stable to the subsequent chemical transformations, and conditions for release from the support should be compatible with the final products. Commonly these linker groups are based on standard protecting groups used in traditional solution-phase synthesis. Trityl groups[1,2] are often used in this context and can serve as protecting groups for alcohols, acids, amides, amines, amino acids, hydroxamic acids, imidazoles, nucleotides, thiols, and thioureas.[1-3] Using a trityl linker in solid-phase synthesis allows the "protected" compound to be subjected to various chemical manipulations followed by release to afford pure compounds without the need for numerous purification steps.[4-7]

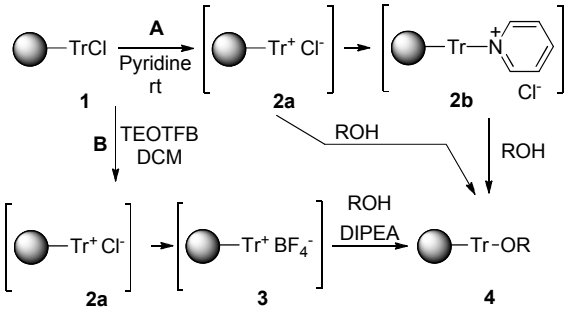
The trityl linker is readily cleaved under mildly acidic conditions (1% TFA in dichloromethane) owing to the high stability of trityl cations.[8] The trityl linker is also orthogonal with protecting groups that can be removed under stronger acidic conditions or basic conditions.[8] However, the formation of trityl ethers has limitations, e.g. some procedures require extensive preparation of reagents,[9,10] while other protocols require prolonged reaction times and harsh conditions and reagents, such as high temperatures or strong bases.[11,12]

Recently, Lundquist et al. published a method employing a silver triflate-assisted attachment of alcohols to a trityl chloride resin.[6] The described procedure enhances the limited reactivity of the standard trityl chloride linker, but suffers from formation of insoluble silver chloride precipitate on the resin and partial degradation of acid-sensitive alcohols. The use of a trityl bromide resin for loading primary alcohols has been reported.[7] This procedure requires ten equivalents of acetyl

bromide (AcBr) for the preparation of polystyrene trityl bromide (PS-TrBr) from a trityl alcohol resin (PS-TrOH). Loading of carboxylic acids[13] and phenols[14] to PS-TrBr has also been reported.

Herein we report an alternative method using three equivalents of triethyloxonium tetrafluoroborate (TEOTFB) for the activation of a trityl resin. We set out to investigate the loading of alcohols onto a pre-activated polystyrene trityl chloride resin (PS-TrCl, **1**). In addition, experiments with loading anilines to the trityl resin were performed, since only a few examples can be found in the literatures.[4] Furthermore, we also became interested in investigating the recycling of the trityl resin. There are a few examples in the literature where PS-TrCl has been recycled (regenerated or reformed) from PS-TrOH using trimethylsilyl chloride[15], acetyl chloride[16] or thionyl chloride[17]. We wanted to be able to recycle the activated resin without formation of PS-TrCl. TEOTFB is commercial available, but is much more expensive than e.g. thionyl chloride. However, TEOTFB can be prepared in a single-step reaction from inexpensive, commercially available, and nonhazardous reagents.[18]

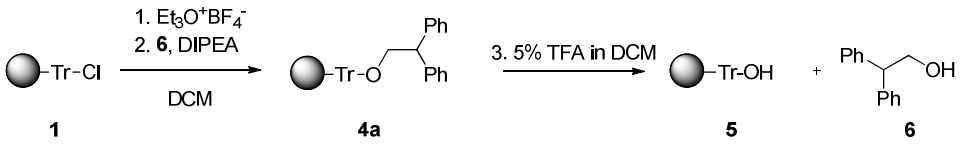
A common method for attaching alcohols to PS-TrCl is to use pyridine both as solvent and base at room temperature (Scheme 1, Path A).[19] Formation of the reactive intermediate **2a** or the pyridinium intermediate (**2b**) is believed to be the rate determining step in the formation of trityl ethers with this method.[9,11,20]



Scheme1. Path **A**: PS-trityl ether (**4**) formation using pyridine; Path **B**: PS-trityl ether formation using triethyloxonium tetrafluoroborate.

We envisioned that treatment of PS-TrCl with TEOTFB could easily generate the more stable trityl cation and would facilitate the S_N1 reaction to form the desired trityl ethers under milder conditions.[21,22] When PS-TrCl (**1**) was treated with TEOTFB (Scheme 1, Path B) a deep red color was initially observed, which indicated formation of the trityl cation. The color disappeared immediately upon addition of alcohol indicating that the cation had been quenched and formation of the trityl ether was complete. The replacement of the chloride counter-anion in **2a** with the more separated ion-pairs formed between the trityl cation and the tetrafluoroborate counter-anion in **3** is believed to enhance the reactivity of the trityl cation.[9,23] We further hypothesized that a nucleophilic attack of the chloride anion on an ethyl group from the triethyloxonium species takes place, which in turn results in the irreversible release of chloroethane gas and thereby facilitating the formation of **3**. In order to establish general conditions that enable an efficient loading of alcohols, the initial focus was set on optimizing the loading of 2,2-diphenylethanol (**6**) onto a commercially available PS-TrCl resin (loading 1.7 mmol/g) using the TEOTFB method. Alcohol **6** was selected as a model substrate based on its UV activity in the range from 200–400 nm. Several reaction parameters were varied, including the amount of TEOTFB, activation time, amount of substrate (**6**), amount of *N,N'*-diisopropylethyl amine (DIPEA) and reaction time (Table 1).

Table 1. Loading of alcohol **6** onto resin **1**[a].



1 **4a** **5** **6**

Entry	TEOTFB (equiv)	Activation (min)	Alcohol **6** (equiv)	DIPEA (equiv)	Loading time (min)	Loading (%)[b]
1	1	15	3	3	180	42
2	2	15	3	3	180	64
3	3	15	3	3	180	88
4	5	15	3	3	60	86
5	3	5	3	3	180	59
6	3	10	3	3	180	69
7	3	30	3	3	60	86
8	3	15	3	3	5	21
9	3	15	3	3	10	24
10	3	15	3	3	60	84
11	3	15	3	3	960	91
12	3	15	1	1	180	49
13	3	15	2	2	180	71
14	5	15	5	5	60	84

[a]300 mg of PS-TrCl (loading 1.7 mmol/g). [b]The loading (%) was quantified by weight of recovered alcohol **6** after cleavage using the resin loading specified by the supplier.

Initially, the amount of TEOTFB needed to activate the trityl resin was investigated (Table 1, entries 1–4). With one or two equivalents of TEOTFB only moderate loading of **6** was obtained. Three equivalents (entry 3) resulted in an loading of 88%. A further increase to five equivalents TEOTFB (entry 4) did not result in a significant enhancement in the loading of **6**.

Variation of the activation time (entries 4–7) revealed that 15 min is required to get a high loading, while shorter time (entries 5–6) reduced the loading of **6**. An extension of the activation time from 15 to 30 min (entry 7) did not result in a substantial increase in loading.

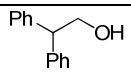
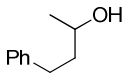
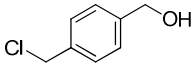
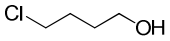
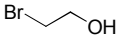
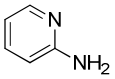
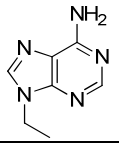
Furthermore, variation of the loading times (entries 8–11) demonstrated that a one hour reaction time (entry 10) is required in order to obtain a high loading of **6**. The loading could be increased to 91 % upon overnight reaction (entry 11).

The amount of alcohol (**6**) and DIPEA (entries 12–14) also have a significant influence on the loading. One or two equivalents of **6** and DIPEA (entries 12 and 13) resulted in moderate loading. Three equivalents of **6** and DIPEA (entry 10) resulted in a loading of 86 %. Additional amounts of **6** and DIPEA (entry 14) did not lead to any further improvement in loading.

In general, from the experiments summarized in Table 1 it was concluded that the optimized reaction conditions are; the use of three equivalents of TEOTFB for activation, the activation is rapid and requires 15 minutes, three equivalents of substrate to be loaded and DIPEA are sufficient for obtaining excellent loadings and the reaction time (loading time) should at least be one hour with the best results obtained when the reaction was performed overnight. The use of large excess of reagents (5–10 equivalents) as in other literature methods, is not required using this protocol.

The TEOTFB activation of resin **1** according to reaction conditions in Entry 11 were then used with a variety of alcohols and aniline derivatives (Table 2).

Table 2. TEOTFB assisted loading of alcohols and aniline derivatives to trityl resin.

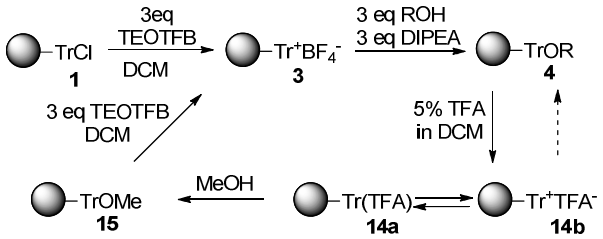
Trityl ether / amine	Alcohol / amine	Yields (%)
6		90
7		63
8		65
9		67
10		74
11		44
12		76
13		46

[a]300 mg of PS-TrCl (loading 1.7 mmol/g). [b]The loading (%) was quantified by weight of recovered substrate (**6**–**13**) after cleavage using the resin loading specified by the supplier.

The trityl ethers from alcohols **6**–**10** using resin **1** activated by TEOTFB, were obtained in yields 63–90% which are comparable to other published procedures.[6] The benefits of performing the trityl ether formation using this protocol include short activation time, use of small amounts of reagents and short reaction times. In addition, no precipitates are formed unlike in previously reported methods.[6]

The favorable results obtained with alcohols prompted adaptation of our new TEOTFB activation method to the solid phase attachment of anilines **11**–**13**. The amines were loaded in moderate to good (44–76%) yields using this protocol. The purity of the obtained compounds **6**–**13** was ascertained by elemental analysis.

The use of trityl resin would become more environmentally friendly and cost effective, especially for large scale applications, if the resin could be recycled. Recycling of hydroxytrityl resins has been reported.[15-17] We anticipated that it should be possible to recycle the trityl resin using TEOTFB activation of PS-TrOMe (**15**) (Scheme 3).



Scheme 2. Efficient recycling of the trityl resin.

Resin **1** was activated with TEOTFB and subsequently reacted with alcohol **6** in the presence of DIPEA for 16h. Excess reagents were washed away and the product was cleaved off with 5% TFA in DCM. After careful washing of the resin with DCM, MeOH was added in order to generate PS-TrOMe (**15**). This material was activated with TEOTFB followed by thorough washing with DCM for the next synthesis cycle. Cleavage of alcohol **6** from the trityl linker using 5% TFA in DCM resulted in a deep red color typical for the formation of a trityl cation (resin **3**). We therefore became interested in exploring the possibility of recycling resin **14**[24] after cleavage of alcohol **6** followed by thorough washing with DCM for the next synthesis cycle. Three cycles were carried out using the same equivalents of reagents in each cycle and the results are summarized in Table 3.

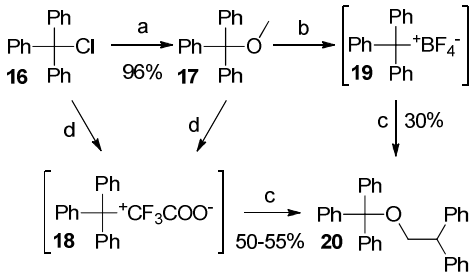
Table 3. Recycling of trityl resin starting from PS-TrOMe or PS-$Tr^{+}TFA^{-}$.

Resin[a]	Loading[b] cycle 1 (%)	Loading[b] cycle 2 (%)	Loading[b] cycle 3 (%)
15	88	79	61
14	86	76	58

[a]300 mg of PS-TrCl (loading 1.7 mmol/g), alcohol **6** (3 equiv) and DIPEA (3 equiv) was used. [b]The loading (%) was quantified by weight of recovered alcohol **6** after cleavage using the resin loading specified by the supplier.

In order to minimize the moisture that reaches the reaction vessels only freshly distilled solvents were used and all reactions and manipulations performed under nitrogen atmosphere. The first cycle resulted in a loading of alcohol **6** in 88%. The loading dropped slightly in the second and third cycles. Similar yields were obtained when starting from **14**.

In order to confirm the correct identity of the intermediates the same reactions were repeated in solution and the isolated products were characterized by NMR spectroscopy and purity confirmed by elemental analysis.



Scheme 3. Reaction pathways for the formation of trityl ethers in solution. a) MeOH, reflux, 3h; b) TEOTFB (0.9 equiv), DCM, 15 min, room temp; c) alcohol **6** (1 equiv); d) TFA (5% in DCM), 15 min, room temp

Trityl chloride (**16**) was refluxed in anhydrous MeOH using a slightly modified literature procedure and methyl trityl ether (**17**) was obtained in 96% yield.[25] When TEOTFB was added to **17** a bright yellow/orange color was observed and the reaction mixture was left for 15 min. The bright yellow color disappeared instantly after addition of alcohol **6** and trityl ether **20** was isolated in 30% yield after purification using column chromatography. Attempts to increase the yield of **20** by increasing the amount of TEOTFB (3 equiv) were unsuccessful due to the formation of an undesired byproduct (*O*-ethylated 2,2-diphenylethanol). This result highlights the advantage of performing this reaction on solid phase, as excess reagents are washed off, the byproduct formation can be avoided. Heating the reaction mixture after the addition TEOTFB to **19**, lead to the formation of triphenylmethane as a byproduct. The formation of trityl ether **20** (50–55% yield) was also demonstrated using TFA (5% in DCM) as a reagent starting from **16** or **17**.

Conclusion

In conclusion, a novel, mild and rapid procedure for the loading of resin-bound alcohols and anilines in good yields has been developed. We envision that the described procedure should be useful e.g. for the solid-phase preparation of peptides containing natural and non-natural amino acids with alcohol functionalities in the side chain as well as for the preparation of modified

heterocycles with aniline functionalities. The protocol offers the advantage of avoiding otherwise long loading times by using a commercial starting resin, which only requires a simple activation prior to the loading step. The resin recycling capability has been demonstrated using this protocol and proposed reaction intermediates have been identified by performing the corresponding reactions in solution.

Experimental Section

General

All commercial chemicals were used as received. DCM was freshly distilled from CaH prior to use. Column chromatography was performed by manual flash chromatography (wet packed aluminum oxide activated, neutral, ~150 mesh). 1H NMR spectra were recorded at 400 MHz and ^{13}C spectra were recorded at 100 MHz.. Melting points are not corrected.

General procedure for triethyloxonium tetrafluoroborate assisted trityl resin loading *Method A*

Trityl resin (300 mg, loading ~1.7 mmol/g) was added to polypropylene fritted tubes, pre-swelled and washed with DCM (3 x 2mL). The resin was put under N_2 atm in sealed tubes. A solution of triethyloxonium tetrafluoroborate (4.4 mL, 0. 35M) was added and the resin was agitated at room temperature for 15 min. The resin was drained and washed thoroughly with DCM (10 x 3 mL) and put under N_2. The substrates **6**–**13** (1.53 mmol, 3 eq) and DIPEA (0.27 mL, 1.53 mmol, 3 eq) were dissolved in DCM (2 mL) and added to the resin. The resin was agitated 16 h at room temperature under N_2 atm, washed with DMF (3 x 3 mL), MeOH (3 x 3 mL), DCM (3 x 3 mL), MeOH (3 x 3 mL) and DCM (3 x 3 mL). The resin was pre-swelled in DCM and TFA (2 mL, 5% in TFA) was

added, the resin was left for 20 min then drained and washed with DCM (2 mL). A second portion of TFA (2 ml, 5% in DCM) was added and the resin was left 5 min then drained and washed thoroughly with DCM (5 x 3 mL) and MeOH (2 x3 mL). If the resin was to be reused it was also washed with DCM (3 x 3 mL) as the final washing step then put under N_2 atm. All washings were combined and the collected residue obtained after cleavage of substrate from the resin was flushed with a stream of N_2 and the solvents were removed under reduced pressure.

2,2-Diphenylethanol (6)

Following method A, **6** (303 mg, 1.53 mmol) was added to the activated resin. Compound **6** was isolated after cleavage from the resin as a white crystalline material in 90% yield (90 mg, 0.45 mmol), m.p. 54–56 °C (lit. 54–55 °C)[26]. ^{1}H and ^{13}C NMR data were in agreement with published data.[6] Anal. Calcd for $C_{14}H_{14}O$: 84.81 (C); 7.12 (H); Found: 84.83(C); 7.13 (H).

4-Phenyl-2-butanol (7)

Following method A, **7** (0.24 mL, 230 mg, 1.53 mmol) was added to the activated resin. Compound **7** was obtained as a colorless liquid in 63% yield (48 mg, 0.32 mmol). ^{1}H and ^{13}C NMR data were in agreement with published data.[6] Anal. Calcd for $C_{10}H_{14}O$: 79.95 (C); 9.39 (H); Found: 79.99 (C); 9.40 (H).

4-(Chloromethyl)benzyl alcohol (8)

Following method A, **8** (240 mg, 1.53 mmol) was added to the activated resin. Compound **8** was obtained as a white crystalline material in 65% yield (52 mg, 0.33 mmol), m.p. 59–61 °C (lit. 58–60 °C[27]). ^{1}H and ^{13}C NMR data were in agreement with published data.[6] Anal. Calcd for C_8H_9ClO: 61.35 (C); 5.79 (H); Found: 61.37(C); 5.81(H).

6-Chloro-1-hexanol (9)

Following method A, **9** (0.20 mL, 209 mg, 1.53 mmol) was added to the activated resin. Compound **9** was obtained as a colorless liquid in 68% yield (47 mg, 0.34 mmol). ^{1}H and ^{13}C NMR data were in agreement with published data.[6] Anal. Calcd for $C_6H_{13}ClO$: 52.75 (C); 9.59 (H); Found: 52.79 (C); 9.61 (H).

2-Bromoethanol (10)

Following method A, **10** (0.10 mL, 198 mg, 1.53 mmol) was added to the activated resin. **10** was obtained as a colorless liquid in 74% yield (47 mg, 0.38 mmol). ^{1}H and ^{13}C NMR data were in agreement with published data.[6] Anal. Calcd for C_2H_5BrO: 19.22 (C); 4.03 (H); Found: 19.24 (C); 4.05 (H).

2-Aminopyridine (11)

Following method A, **11** (144 mg, 1.53 mmol) was added to the activated resin. **11** was obtained as a beige crystalline material in 44% yield (21 mg, 0.22 mmol), m.p. 55–59 °C (lit. 54–58 °C[28]). ^{1}H and ^{13}C NMR data were in agreement with published data.[6] Anal. Calcd for $C_5H_6N_2$: 63.81 (C); 6.43 (H); 29.77 (N); Found: 63.84 (C); 6.45 (H); 29.79 (N).

Aniline (12)

Following method A, **12** (0.14 mL, 143 mg, 1.53 mmol) was added to the activated resin. The TFA salt of **12** was obtained as a beige crystalline material in 76% yield (80 mg, 0.39 mmol), m.p. 119–121 °C (lit. 120 °C)[29]. ^{1}H and ^{13}C NMR data were in agreement with published data.[6] Anal. Calcd for $C_8H_9F_3NO_2$: 46.16 (C); 4.36 (H); 6.73 (N); Found: 46.18 (C); 4.35 (H); 6.75 (N).

9-Ethyladenine (13)

Following method A, **13** (250 mg, 1.53 mmol) was added to the activated resin. Compound **13** was obtained as a white crystalline material in 46% yield (38 mg, 0.23 mmol), m.p. 194–197 °C (lit. 195-197 °C).[30] ^{1}H and ^{13}C NMR data were in agreement with published data.[6] Anal. Calcd for $C_7H_9N_5$: 51.52 (C); 5.56 (H); 49.92 (N); Found: 51.53 (C); 5.57 (H); 49.95 (N).

Methyl triphenylmethyl ether (17)

Using a modified literature procedure[25] trityl chloride (558 mg, 2.0 mmol) and methanol (15 mL) were refluxed at 105 °C for 3 h under N_2 atm. The solvent was removed under reduced pressure and **17** was obtained as white crystalline material in 99% yield (546 mg, 2.0 mmol), m.p. 82–84 °C (lit. 82 °C). ^{1}H and ^{13}C NMR data were in agreement with published data.[31,32]

(2,2-Diphenylethoxy)triphenylmethyl ether (20)

Method B

Triethyloxonium tetrafluoroborate (62.3 mg, 0.33 mmol) was suspended in DCM (1 mL) and added to a solution of **17** (100 mg, 0.37 mmol) in DCM (1 mL). The bright yellow reaction mixture was stirred 15 min at room temperature under N_2 atm, thereafter a solution of 2,2-diphenylethanol (**6**)

(72.3 mg, 0.37 mmol) in DCM (1mL) was added and the reaction mixture turned colorless. After stirring for 1 h under N_2 atm the reaction was quenched by the addition of water (3 mL), the aqueous layer extracted with DCM (3 x 5 mL), the combined organic layers were dried over $MgSO_4$ and solvent removed under reduced pressure. The residue was purified using flash chromatography (2% DCM in heptane) and **20** was obtained as white crystalline material in 33% yield (48.0 mg, 0.11 mmol).

Method C

TFA (1 mL, 5% in DCM) was added to **17** (100 mg, 0.37 mmol). The bright yellow reaction mixture was stirred 15 min at room temperature under N_2 atm, thereafter a solution of **6** (86.7 mg, 0.44 mmol) in DCM (1mL) was added and the reaction mixture turned colorless. After stirring for 1 h under N_2 atm the reaction was quenched by the addition of water (3 mL), the aqueous layer extracted with DCM (3 x 5 mL), the combined organic layers were dried over $MgSO_4$ and solvent removed under reduced pressure. The residue was purified using flash chromatography (2% DCM in heptane) and **20** was obtained as white crystalline material in 50% yield (80.0 mg, 0.18 mmol).

Method D

TFA (2 mL, 5% in DCM) was added to triphenylchloromethane (**16**) (300 mg, 1.08 mmol). The bright yellow reaction mixture was stirred 15 min at room temperature under N_2 atm, thereafter a solution of **6** (214 mg, 1.08 mmol) in DCM (1mL) was added and the reaction mixture turned colorless. After stirring for 1 h under N_2 atm the reaction was quenched by the addition of water (3 mL), the aqueous layer extracted with DCM (3 x 5 mL), the combined organic layers were dried over $MgSO_4$ and solvent removed under reduced pressure. The residue was purified using flash

chromatography (2% DCM in heptane) and **20** was obtained as white crystalline material in 55% yield (262 mg, 0.60 mmol), m.p. 38–40 °C. ^{1}H and ^{13}C NMR data were in agreement with published data.[6]

Recycling of resin using TEOTFB method

Following method A, **6** (303 mg, 1.53 mmol) was added to the activated resin. The resin was regenerated two times and the procedure was performed for the total of three times with the same batch of resin. The first cycle the resin was agitated 3 h, second cycle 3 h and third cycle 3 h. **6** was obtained as white crystalline material in 88% yield (89 mg, 0.45 mmol), the second cycle in 79% (80 mg, 0.40 mmol) and the third cycle in 61% (62 mg, 0.31 mmol), m.p. 54–56. °C (lit. 54–55 °C).[26] ^{1}H and ^{13}C NMR data were in agreement with published data.[6] Anal. Calcd for $C_{14}H_{14}O$: 84.81 (C); 7.12 (H); Found: 84.83(C); 7.13 (H).

Recycling of resin using TFA method

Trityl resin (300 mg, loading ~1.7 mmol/g) was added to polypropylene fritted tubes, pre-swelled and washed with DCM (3 x 2mL). The resin was put under N_2 atm in sealed tubes. TFA (2 mL 5% in DCM) was added and the resin was agitated at rt for 15 min. The resin was drained and washed with DCM (3 x 3 mL) and put under N_2. A mixture of **6** (303 mg, 1.53 mmol) and DIPEA (0.27 mL, 1.53 mmol) in DCM (2 mL) was added to the resin. The resin was agitated 3 h at rt under N_2 atm, washed with DMF (3 x 3 mL), MeOH (3 x 3 mL), DCM (3 x 3 mL), MeOH (3 x 3 mL) and DCM (3 x 3mL). The resin was pre-swelled in DCM and TFA (2 mL, 5% in DCM) was added, the resin was left for 20 min then drained and washed with DCM (2 mL). A second portion of TFA (2 ml, 5% in DCM) was added and the resin left 5 min then drained and washed thoroughly with DCM

(5 x 3 mL) then put under N_2 atm. The procedure was performed for the total of three times with the same batch of resin. The second time the resin was agitated 3 h and the third cycle 3 h. The collected residue obtained after cleavage of substrate from the resin was flushed with a stream of N_2 and the solvents were removed under reduced pressure. **6** was obtained as white crystalline material in 86% yield (87 mg, 0.44 mmol), the second cycle in 76% (77 mg, 0.39 mmol) and the third cycle in 58% (59 mg, 0.30 mmol), m.p. 54–56. °C (lit. 54–55 °C).[26] ^{1}H- and ^{13}C- NMR data were in agreement with published data.[6] Anal. Calcd for $C_{14}H_{14}O$: 84.81 (C); 7.12 (H); Found: 84.83(C); 7.13 (H).

Acknowledgment

We are grateful to the Department of Chemistry at University of Gothenburg, the Swedish Academy of Pharmaceutical Sciences and the Swedish Research Council (project # 62120083533) for financial support.

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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