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LETTERS

Efficient synthesis of benzylic bromides under neutral conditions on solid support

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Abstract

A method of benzylic alcohol bromination on solid phase in neutral conditions was developed. Its application to the preparation of brominated linkers is described. © 2000 Elsevier Science Ltd. All rights reserved.

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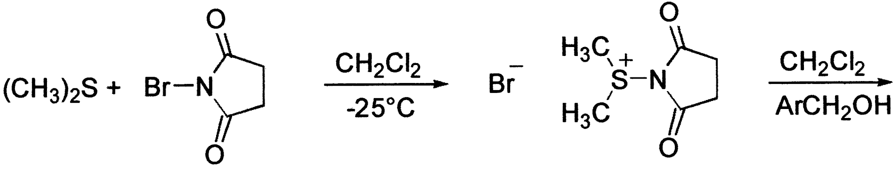
Most commercially available resins with a cleavable linker include a benzylic alcohol.[1] In order to use or to modify such linkers the benzylic alcohols need activation. For most purposes a benzylic bromide would be a suitable group, which have enough stability and reactivity to be used in solid phase synthesis. Brominations of such benzylic linkers were already described using reagents such as triphenylphosphine dibromide[2] or thionylbromide,[3] which generate hydrobromic acid. Thus, the released acid or the reagent ($PPh_3 \cdot Br_2$) might cleave the linker in several cases.[4] Some bromination of benzylic alcohol under neutral conditions were described in solution using triphenylphosphine and carbon tetrabromide.[5] With this later method, reaction of benzylic bromide and triphenylphosphine occurred in some extent to give a phosphonium salt.[4] An alternative method could be the use of *N*-bromosuccinimide and dimethylsulfide. This method was described by E. J. Corey and coll. to convert allylic and benzylic alcohols into bromides (Scheme 1).[6]



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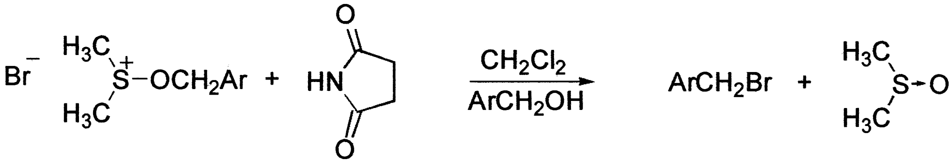
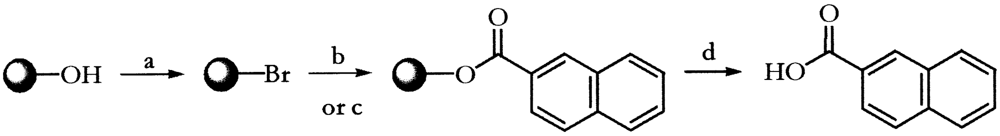


Scheme 1.

Corey's procedure is a good candidate for solid phase synthesis because the reagents excess would not react with the reaction products. Moreover, in solid phase chemistry, since the benzylic bromide will be on the resin, the excess of reagents and the other products formed (DMSO and succinimide) could be removed by several washings with anhydrous solvents to avoid benzylic bromide hydrolysis.

One way to quantify the loading of the new brominated resin is to use a chemical reaction that is specific for the new linker, has a quantitative yield and produce, after the cleavage, a quantifiable compound. To achieve this goal we decided to substitute the benzylic bromides with a salt of 2-naphthoic acid. The experiment is summarised in Scheme 2.

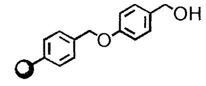
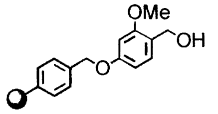
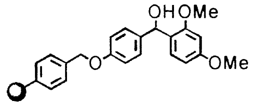
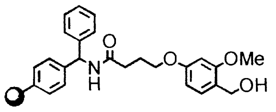
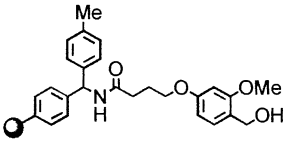
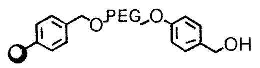
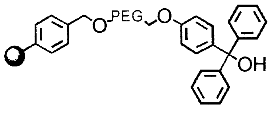
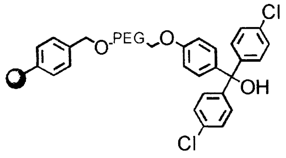


Scheme 2. Reagents and conditions: (a) NBS (0.4–0.5 M), CH_3SCH_3 (0.4–0.5 M), CH_2Cl_2, 0°C; (b) Method A: $C_{10}H_7OO^-Cs^+$ (20 equiv.), dibenzo-18-crown-6 (20 equiv.), DMA, 60°C, 5 h; (c) Method B: $C_{10}H_7COOH$ (20 equiv.), DIPEA (40 equiv.), CH_2Cl_2, 20 h, rt; (d) TFA (1–50%), rt, 3×15 min

The resin with a known loading was treated with an excess of the complex NBS/dimethylsulfide prepared as a 0.4–0.5 M dichloromethane solution.[7] Washing the resin afforded the brominated linker, which was treated with a salt of 2-naphtoic acid to afford the corresponding ester. To eliminate the factor of substitution yield we have tried two methods to introduce 2-naphtoic acid using the caesium[8] and the diisopropylethylammonium[9] salts, respectively. Treatment of the resin bound ester with trifluoroacetic acid in dichloromethane afforded 2-naphtoic acid. Determination of the amount of 2-naphtoic acid released gave the brominated resin loading. The results of the different experiments are reported in Table 1.

Since the preparation of esters with trityl chloride or benzhydryl chloride type linkers were already described,[10] we conclude that for entries 3, 7 and 8 the linker brominations were unsuccessful. The conversion into bromide was quantitative only with benzylic alcohols and the resin could be modified and used without a capping procedure.

Table 1

Entry	Resin	Loading (meq./g)	Resin structure	2- Naphtoic acid Method A[a] yield%[b]	2- Naphtoic acid Method B[a] yield%[b]
1	Wang resin (100-200 mesh)	1,45		86%	98%
2	SASRIN® resin (100-200 mesh)	0,93		98%	98%
3	Rink acid resin (100-200 mesh)	0,52		5%	30%
4	HMBP-BHA resin (100-200 mesh)	0,59		98%	98%
5	HMBP-MBHA resin (100-200 mesh)	0,51		98%	98%
6	NovaSyn TG HMP resin (90μm)	0,26		90%	90 %
7	NovaSyn Trityl alcohol resin (130μm)	0,18		0%	0%
8	NovaSyn Dichlorotrityl alcohol TG resin (130μm)	0,19		0%	0%

a) the brominated resin is treated in IRORI macro-Kans® with 2-naphtoic acid caesium salt (20 eq.) and dibenzo-18-crown-6 (20 eq.) during 5 hours at 60°C in dimethylacetamide (Method A) or with 2-naphtoic acid diisopropylethylammonium salt (20 eq.) during 20 hours at room temperature in dichloromethane (Method B), the Kans® are washed as described in reference 7 ; b) the esterified resin is treated three times with a mixture of trifluoroacetic acid and dichloromethane to give pure 2-naphtoic acid (LC/MS) ; the yields were calculated from the hydroxylated resin.

Acknowledgements

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7. Typical procedure to prepare bromo-SASRIN® resin: NBS (16.6 g, 93 mmol) is suspended in anhydrous methylene chloride (200 mL). The slurry was cooled under argon to 0°C and dimethylsulfide (7.5 mL, 102.30 mmol) was added dropwise. The resulting mixture was stirred at 0°C for 20 min. To the yellow solution obtained, 10 IRORI macro-Kans®, containing each 200 mg of SASRIN® resin (0.93 mequiv./g), were added and the mixture was smoothly stirred at 0°C under argon for 5 hours. The solution was stripped off, the Kans® were successively washed with anhydrous methylene chloride, THF, 1,4-dioxane, THF and methylene chloride. Drying under vacuum gave Kans® that was ready to be used. The amount of reagents and solvents are calculated to have a concentration of about 0.4–0.5 M and to cover all the Kans® with the reagent solution (about 50 equiv. of reagents). If loose resin was used, less liquid was needed to cover the resin at similar concentration of reagents.
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