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Efficient Synthesis of Bromoacetylated Wang resin

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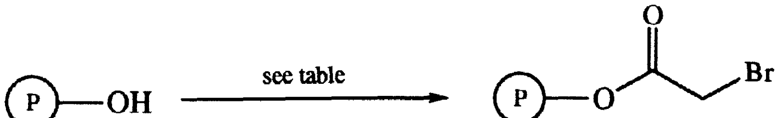
Abstract : The alcohol groups linked to different polymers have been subjected to bromoacetylation either by alcohol activation (under Mitsunobu conditions) or by several acid- activation methods. By far the best result for Wang resin was obtained with the first strategy. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Bromoacetylated resins (specially Wang resin) are versatile starting materials useful in the solid phase synthesis of carboxymethyl compounds attainable through nucleophilic displacement of the bromine ion by amines, thiols... At the final step a smooth cleavage from the polymer can be performed by TFA acidolysis of the ester bond yielding the target molecule.

Our first attempts using different acid activation procedures of $BrCH_2COOH$ were very disappointing for Wang resin (See Table) whereas bromoacetyl bromide (7 fold molar excess) led to a nearly quantitative coupling of a soluble HO-PEG polymer and of an HO-PEG-PS resin. Moreover, it is noteworthy that in our hands as well as for others in our laboratory, the DCC-catalytic DMAP activation system was inefficient in Wang resin esterification, contrary to published results[1] using the very similar DIC-catalytic DMAP one (in both cases the true activated species seems likely to be the acyl-pyridinium intermediate). In the presence of pyridine, DIC activation of bromacetic acid yielded a Wang resin α-pyridinium acetate after acylation and pyridine-bromine substitution[2].

Instead of pursuing in this way, we decided not to activate the acid moiety which contains two reactive groups but to move to the resin alcohol activation. Mitsunobu reaction conditions are well adapted to polymer support chemistry and many reactions such as etherifications[3-4], esterification of N-protected amino acids[4-5] or synthesis of hydroxamic acids[6] have been carried out efficiently. The often tedious elimination of the phosphine oxide by-product in solution synthesis is avoided here by a simple filtration step.



1, 2, 3

1 : Wang resin : HO-CH_2-$_pC_6H_5$-$OCH_2C_6H_5$ —(PS)
2 : Polyethylene glycol : HO-$(C_2H_4O)_m$-H
3 : TG-HMP resin : HO-CH_2-$_pC_6H_5$-$(OC_2H_4)_n$-$OCH_2C_6H_5$ —(PS)

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Resin or polymer	DCC/DMAP $BrCH_2CO_2H$	IBCF/Et_3N $BrCH_2CO_2H$	Et_3N $BrCH_2COBr$	PPh_3/DEAD $BrCH_2CO_2H$
1 : Wang resin[7]	< 10[a]	< 10[a]	< 10[a]	86
2 : PEG polymer[8]	by product[b]	42	95	-
3 : TG-HMP resin	-	-	75	85

a : estimated by IR analysis. b : identified as p-dimethylaminopyridinium-acetyl-PEG

Table : Yield of isolated compounds.

Fortunately, the bromacetylation of Wang resin was well achieved by alcohol activation using the Mitsunobu reaction, which was also efficiently applied to PEG-PS resin. Since the latter, showing the same terminal hydroxybenzylic function, can be as well acylated by both activation procedures (see Table), a lack of accessibility could explain the inefficiency of the acid-activated species toward the OH groups of the Wang resin.

To conclude, bromacetyl-Wang resin, a useful starting material for combinatorial chemistry, is readily and conveniently prepared by a Mistunobu reaction.

References and notes

abbreviations : TFA, trifluoroacetic acid ; DCC, dicyclohexylcarbodiimide ; DIC, Diisopropylcarbodiimide ; DMAP, dimethylaminopyridine ; PEG, polyethyleneglycol, PS, cross-linked polystyrene, IBCF, isobutyl chloroformate ; $P(Ph)_3$/DEAD, Triphenylphosphine/diethylazodicarboxylate

1 : Scott B.O., Siegmund A.C., Marlowe C.K., Pei Y., Spear K.L., *Mol. Diversity* **1995**, 1, 125-134.
2 : Vo N.H., Eyermann C.J., Hodge C.N., *Tetrahedron Lett.* **1997**, 38, 7951-7954.
3 : Rano T.A., Chapman K., *ibid* **1995**, 36, 3789-92.
4 : Krchnak V., Flegelova Z., Weichsel A.S., Lebl M. *ibid*, **1995**, 36, 6193-6196.
5 : Sieber P. *ibid*, **1987**, 28, 6147-6150.
6 : Floyd C.D., Lewis C.N., Patel S.R., Whittaher M. *ibid*, **1996**, 37, 8045-8048.

7 : Synthesis of **1** : To a mixture of Wang resin (0.5 g, 0.69 meq OH/g, 100-200 mesh) , $BrCH_2CO_2H$ (0.24 g, 1.73 mmoles) and triphenylphosphine (0.45 g, 1.73 mmoles) in 8ml of anhydrous THF under an argon atmosphere was added dropwise DEAD (0.27ml, 1.73 mmoles) diluted with 2ml of THF. The resulting resin suspension was gently stirred at 20°C for 24 hours, then the polymer was filtered, washed three times with THF and CH_2Cl_2 to give the resin **1**, yield=86% (calculated on Br %). The product absorbed strongly at 1735 cm^{-1} (ester band). C,H,Br, : 83.56%(C), 7.12%(H), 5.09%(Br) ; found : 83.77%(C), 6.97%(H), 4.40%(Br).

8 : Synthesis of **2** : To a solution of PEG_{3400} (1g, 2.94 10^{-4}moles) in 5ml of dry dichloromethane was added at -20°C $BrCH_2COBr$ (0.17ml, 1.94 mmoles) and triethylamine (0.082ml, 2.94 10^{-4}moles). The resulting solution was stirred at 20°C for one day, then the solvent was evaporated under reduced pressure to give an oil, after precipitation of Et_3N,HBr in ethyl acetate, the polymer **2** was precipitated in cold ethyl acetate to give a white solid (1.02 g, yield=95%). This product absorbed strongly at 1738 cm^{-1} (ester band). ^{1}H-NMR ($CDCl_3$) at 250 MHz : δ (ppm) : 3.50-3.85 (m, H PEG), 3.90 (s, 4H), 4.30-4.40 (m, 4H).