Pergamon

Tetrahedron Letters 39 (1998) 8533–8536

TETRAHEDRON LETTERS

Merrifield, Alpha-MethoxyPhenyl (MAMP) Resin; A New Versatile Solid Support for the Synthesis of Secondary Amides.

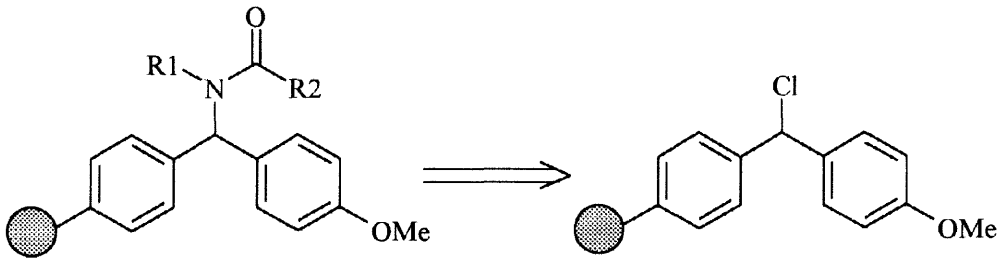
Dearg S. Brown,*[1] John M. Revill and Richard E. Shute

Lead Discovery Department, Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.

Received 5 May 1998; accepted 7 September 1998

Abstract: The synthesis and initial reactivity of a new resin, termed MAMP (Merrifield, Alpha-Methoxy Phenyl), which is useful for the on-resin synthesis and mild acidolytic cleavage of compounds containing secondary amide functionality, is reported. Synthesis of a model peptoid utilising MAMP-resin is described.

In the rapidly growing field of combinatorial chemistry there has been an increasing need to develop new types of solid supports and novel linkers in order to facilitate the synthesis of non-peptides. The choice of cleavage point and the nature of the residual functional group left after cleavage are key issues in the design of solid phase synthesis (SPS) approaches to libraries. Ideally, no vestige of the linker should remain in the library products and consequently a number of new systems have been reported where cleavage leads to replacement of the linker functionality with a proton: so-called 'traceless' linkers.[2] In this communication we report a new amine-based resin for SPS that is based on methylbenzhydrylamine (MBHA) resin,[3] and which, on acylation and cleavage by mild acidolysis, yields secondary amide containing products wherein the only vestige of the linker is the proton of the secondary amide.[4] This resin was designed to circumvent some of the undesirable properties associated with the known linkers for primary amides, for example: the presence of potentially unstable benzyl ether linkages (as found in Rink resin[5]), reactive secondary amides as part of the resin-linker structure (as in PAL resin[6]); the need for a separate and tedious synthesis of the linker moiety; and addition of extra bulk to the resin which results in reducing the overall loading of the resin. Furthermore, the resin was designed to start from the benzhydryl chloride[7] rather than the benzhydryl amine so that a wider variety of diverse amines (R^1-NH_2) could be attached.

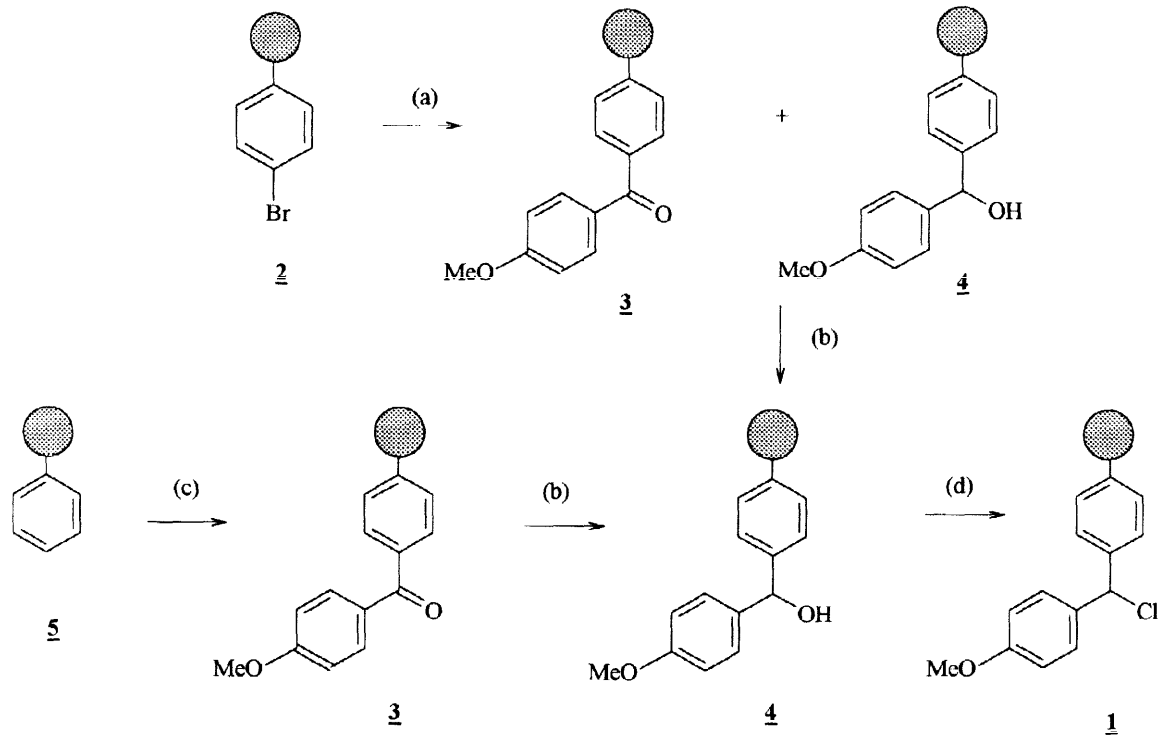


1

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01892-9

From our investigations of a number of systems we found that substituting cross-linked chloromethylpolystyrene (Merrifield resin) with an *alpha*-methoxyphenyl group to give MAMP resin, **1**, provided the best balance of the properties we were seeking, namely: general chemical stability but mild acid lability; good loading levels (≈ 1 mmol/g); easy preparation; and a synthesis that was amenable to large-scale production.

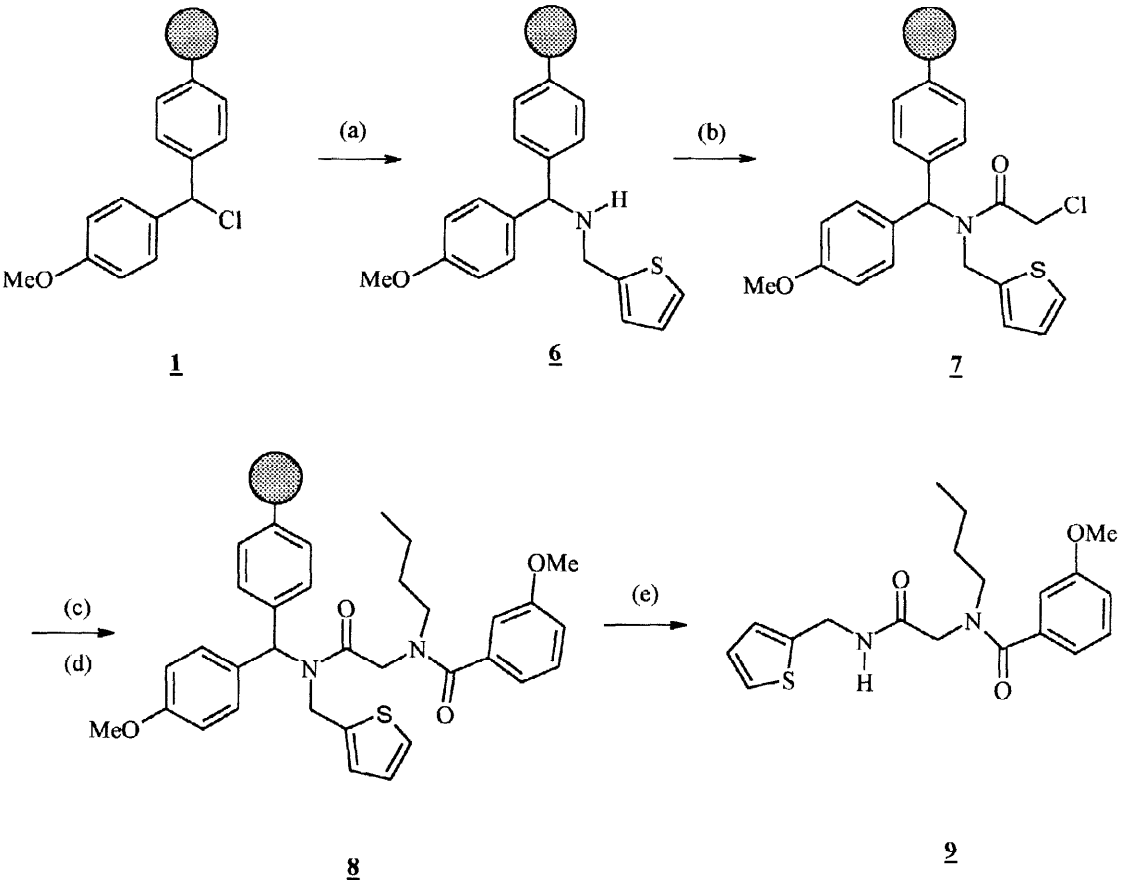
Our initial synthesis of **1** involved lithiation of bromopolystyrene **2**[8] and reaction with 4-methoxybenzaldehyde (**Scheme 1**).[9] This gave, somewhat surprisingly, a mixture of the desired benzhydryl alcohol, **4**, and the benzophenone **3**,[10] which presumably arises *via* a type of Oppenauer oxidation[11] of the initially formed **4** by the excess benzaldehyde. Borohydride reduction of the mixture of **3** and **4** gave purely the supported benzhydryl alcohol **4**, which was chlorinated by treatment with acetyl chloride to give **1**. In order to avoid the keto-alcohol mixture generated by this route, alternative syntheses of MAMP resin were investigated. Most conveniently, polystyrene, 1% cross-linked with divinylbenzene, **5**, was acylated[12] with anisoyl chloride in the presence of ferric chloride to give purely **3**. Borohydride reduction followed by chlorination with acetyl chloride yielded **1** with a substitution level (determined by chlorine elemental analysis)[13] generally between 1 and 2 mmol/g.



Scheme 1: (a) nBuLi, $PhCH_3$, 60°C then 4-(MeO)PhCHO, THF, r.t.; (b) $LiBH_4$, THF, 60°C; (c) $FeCl_3$, CH_2Cl_2, 4-(MeO)PhCOCl, r.t.; (d) CH_3COCl, $PhCH_3$, 60°C.

In order to demonstrate the utility of MAMP resin, we undertook initially the syntheses of some model *N*-substituted glycine structures or "peptoids",[14] one example of which is shown in **Scheme 2**.[15]
Hence, amination of **1** with an excess of 2-thiophenemethylamine gave supported secondary amine **6**, as evidenced by the absence of chlorine on elemental analysis of the resin.[13] Acylation of MAMP-amine resins such as **6** was found to proceed optimally using acyl chlorides. So, reaction of **6** with chloroacetyl chloride gave **7**,

which, by elemental analysis showed a molar S : N : Cl ratio of 1 : 1 : 1 indicating that no bis-alkylative cross-linking had occurred during the previous reaction. Amination with 1-butylamine, again in excess, followed by acylation with 3-methoxybenzoyl chloride gave **8**. Acidolysis of **8** was achieved with 9% TFA in CH_2Cl_2, with a trace of water as scavenger, to give the product, **9**, in 49% yield and in over 90% purity by hplc.



1 **6** **7** **8** **9**

Scheme 2: (a) 2-thiophenemethylamine, NMP, r.t., 48 h; (b) $ClCH_2COCl$, pyridine, THF, r.t., 16 h; (c) n-butylamine, NaI, NMP, 80°C, 16 h; (d) 3-(MeO)PhCOCl, THF: pyridine (1 : 1), r.t., 16 h; (e) 90:9:1, CH_2Cl_2:TFA:H_2O, r.t., 1 h.

Using very similar reaction conditions,[15] we have attached amines as diverse as anilines (eg. 3-chloroaniline and 4-methoxyaniline), α-substituted aliphatic amines (eg. isopropylamine and cyclohexylamine) and functionalised amines (eg. *N,N*-dimethylethylenediamine), then acylated the resultant resin-bound secondary amines with acid chlorides (eg. α-chlorophenylacetyl chloride, phenylacetyl chloride, methyl oxalyl chloride and 4-iodobenzoyl chloride).[13] Recognising that the above cleavage conditions may not have been optimal, we examined more closely the cleavage conditions for these amide product-resins, which are similar in structure to **7**. These studies indicated that optimal product recovery and purity is obtained by treatment of MAMP amide-resins with a CH_2Cl_2:TFA:H_2O, 75:23:2 mixture for 1 h at room temperature. Under these cleavage conditions all of the MAMP amide-resins alluded to above uniformly yielded products in ≥ 70% yield and in >90% purity.

In conclusion, we have reported the synthesis and initial reactivity of a new versatile resin, termed MAMP, which has broad utility for the on-resin synthesis and mild acidolytic cleavage of compounds containing secondary amide functionality.

References and Notes

1. The authors acknowledge the contributions of David Pears and Bruce Denton to this work.
2. (a) Plunkett, M. J.; Ellman, J., *J. Org. Chem.* **1995**, *60*, 6006. (b) Chenera, B.; Finkelstein, J. A.; Veber, D. F., *J. Am. Chem. Soc.* **1995**, *117*, 11999. (c) Hone, N. D.; Davies, S. G., Devereux, N. J.; Taylor, S. L.; Baxter, A. D. *Tetrahedon Lett.* **1998**, *39*, 897. (d) Hu, Y.; Porco, J. A.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518.
3. Matsueda, G.R.; Stewart, J.M. *Peptides* **1981**, *2*, 45. Channabasavaiah, K.; Stewart, J.M. *Biochem. Biophys. Res. Commun.* **1981**, *86*, 45.
4. (a) Katritzky, A. R.; Xie, L. H.; Zhang, G. F.; Griffith, M.; Watson, K.; Kiely, J. S. *Tetrahedon Lett.* **1997**, *38*, 7011. (b) Fivush, A. M.; Willson, T. M. *Tetrahedon Lett.* **1997**, *38*, 7151. (c) Sarantakis, D.; Bicksler, J. J. *Tetrahedon Lett.* **1997**, *38*, 7325-8. (d) Brown, E. G.; Nuss, J. M. *Tetrahedron Lett.* **1997**, *38*, 8457. (e) Swayze, E. E. *Tetrahedron Lett.* **1997**, *38*, 8465. (f) Jensen, K. J.; Alsina, J.; Songster, M. F.; Vagner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441.
5. Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787.
6. Albericio, F.; Kneib-Cordonier, N.; Biancalana, S.; Gera, L.; Masada, R. I.; Hudson, D.; Barany, G. *J. Org. Chem.* **1990**, *55*, 3730.
7. For other uses of polymer-supported benzhydryl chlorides see: (a) Canne, L. E.; Walker, S. M.; Kent, S. B. H. *Tetrahedon Lett.* **1995**, *36*, 1217. (b) Garigipati, R.S. *Tetrahedron Lett.* **1997**, *38*, 6807.
8. Farrall, J.M.; Frechet, J.M. *J. Org. Chem.* **1976**, *41*, 3877.
9. Abbreviations: NMP = *N*-methylpyrrolidone; THF = tetrahydrofuran; TFA = trifluoroacetic acid; r.t. = room temperature.
10. As indicated by the presence of a carbonyl absorption at 1649 cm^{-1} in the FT-IR of a mull of the resin in $CHCl_3$.
11. For a review of the Oppenauer oxidation, see Djerassi, C. *Org. React.* **1951**, *6*, 207.
12. Zicos, C.C.; Frederigos, N.G. *Tetrahedron Lett.* **1995**, *36*, 3741.
13. Resins were routinely analysed by elemental analysis for heavy elements, by FT-IR for (dis)appearance of functional groups and by cleavage and analysis of the resultant products by NMR, mass spectrometry and hplc.
14. Goff, D.A.; Zuckerman, R.N. *J. Org. Chem.* **1995**, *38*, 1427.
15. Typical procedure: To **1** (55.43 g; found: Cl, 7.0% corresponding to a loading of 1.97 mmol/g) swollen in THF (500 mL) was added dropwise 2-thiophenemethylamine (123 g) in THF (250 mL). The reaction was shaken at room temperature for 48 h. The resin was then filtered, washed in turn with DMF, THF, MeOH and dried under vacuum to give **6** (70 g; found: C, 79.6%; H, 7.2%; N, 2.3%; S, 5.2%; Cl, 0% corresponding to a loading of 1.62 mmol/g). To **6** (1 g) swollen in THF (10 mL) was added pyridine (0.38 mL) followed by chloroacetyl chloride (0.33 mL). The reaction was shaken overnight at room temperature, filtered and the resin was washed with 2:1 THF: H_2O, THF, MeOH then dried under vacuum, to give **7** (1.27 g; found: C, 71.8%; H, 6.4%; N, 2.0%; S, 4.4%; Cl, 5.4% corresponding to a loading of 1.5 mmol/g; FT-IR ($CHCl_3$ mull) 1651 cm^{-1}). To **7** (1 g) in NMP (8 mL) was added 1-butylamine (1.6 mL) and sodium iodide (25 mg). The reaction was shaken at 80°C overnight then allowed to cool to room temperature, filtered and the resin washed in turn with NMP, THF, MeOH and dried under vacuum (Yield: 1.04 g; found: C, 75.5%; H, 7.6%; N, 3.9%; S, 4.3%; Cl, 0%). To this resin (0.9 g) in THF (10 mL) was added pyridine (0.8 mL) followed by 3-methoxybenzoyl chloride (1.1 mL). The reaction was shaken overnight at room temperature then filtered, washed in turn with 2:1 THF:H_2O, THF, MeOH and dried under vacuum to yield **8** (1.02 g; found: C, 76.3%; H, 7.0%; N, 3.3%; S, 3.7% corresponding to a loading of 1.15 mmol/g). To **8** (0.22 g) was added a mixture of CH_2Cl_2:TFA:H_2O, 90:9:1 (5 mL). The cleavage mixture was shaken at room temperature for 1 h, filtered and the filtrate evaporated to dryness to give **9** (45 mg; 49% yield based on the loading of **8**) as a straw gum (Found: MH^+, 361; δ-DMSOd_6: 0.80 (m, 3 H), 1.20 (m, 2H), 1.50 (m, 2H), 3.30 (m, 2H), 3.73 (s, 3H), 3.95 (s, 2H), 4.48 (d, 2H), 6.90 (m, 5H), 7.30 (m, 2H), 8.05 (bs, 1H) with a 93% purity by hplc.