Pergamon

Tetrahedron Letters, Vol. 38, No. 39, pp. 6807-6810, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01600-6

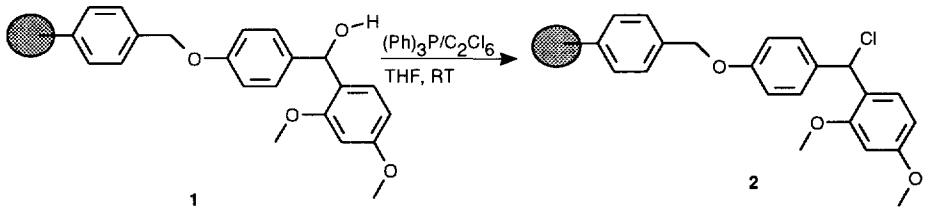
Reagents For Combinatorial Organic Synthesis: Preparation and Uses of Rink-Chloride

Ravi S. Garigipati

Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19046-0939, USA.

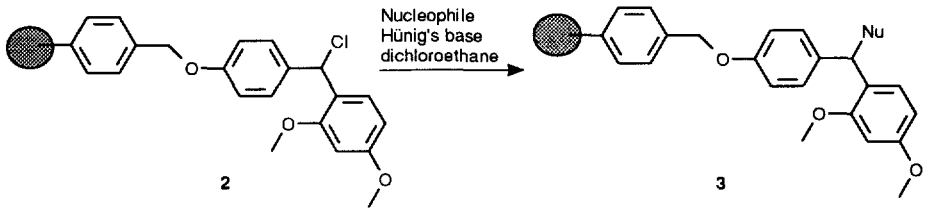
Abstract: The preparation of Rink-chloride and its utility in attaching various nucleophiles to a solid support are described. © 1997 Elsevier Science Ltd.

Chemical synthesis on solid supports has become a cornerstone in the generation of small organic molecule libraries.[1] Paramount to the success of any solid-phase synthetic strategy is a reliable and general method for coupling the initial starting materials onto the solid support. Such a linker should also be amenable to ready cleavage of the reaction products under relatively mild conditions. The Rink linker[2] has been effectively applied to the synthesis of some chemical libraries[3] because mild conditions suffice for release of the library components. However, the Rink technology is currently limited to the preparation of amides and carboxylic acids.[4] Herein, we describe the preparation and utility of Rink-chloride, which allows a very general and practical method for the attachment of amines, alcohols and thiols to a solid support and also their release under mild conditions.



1 2

Scheme I



Scheme II

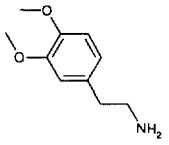
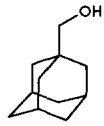
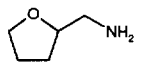
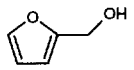
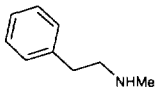
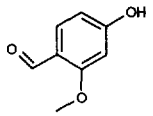
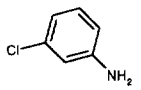
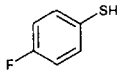
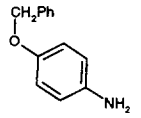
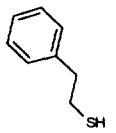
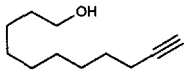
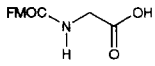
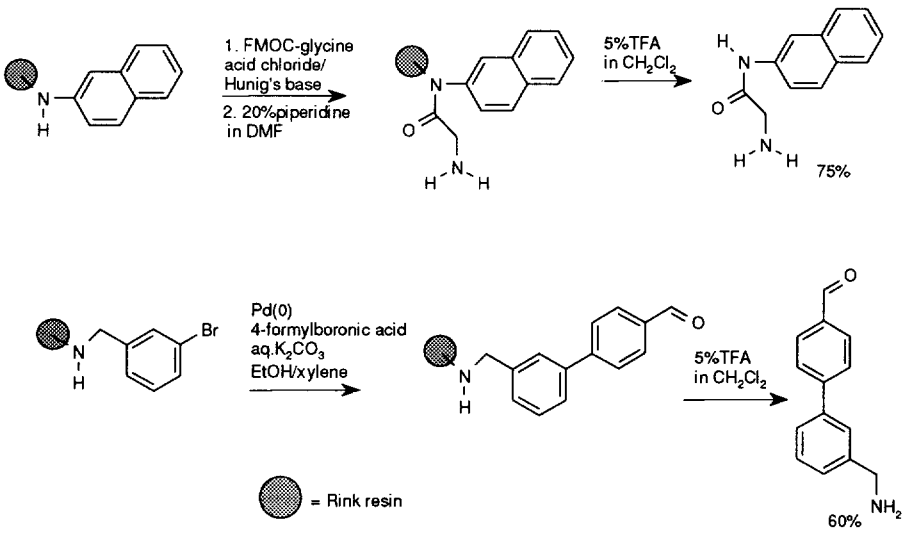
#	Nucleophile	Yield	Purity	#	Nucleophile	Yield	Purity
1		95	93	7		90	95
2		94	90	8		85	80
3		95	96	9		96	91
4		90	94	10		84	90
5		95	95	11		92	95
6		85	95	12		96	95

Table I

Rink-acid[5] resin **1** can be converted to the Rink-chloride **2** upon treatment with triphenyl phosphine and hexachloroethane (Scheme **I**).[6,7,8] The resin so obtained is stable at room temperature for several days and can be used without any loss of activity. Rink-chloride can be reacted cleanly with a variety of nucleophiles under mild reaction conditions (Scheme II). Rink-chloride efficiently reacts with primary and secondary amines, anilines, alcohols, phenols, thiols, thiophenols and carboxylic acids. The coupling is usually carried out in dichloroethane in the presence of Hünig's base, under an inert atmosphere for 18-36 hours at room temperature.[9] The extent of coupling efficiency can be monitored by Magic Angle Spinning NMR (MAS NMR)[10] and quantitated by cleaving the product from the resin with 5% TFA in CH_2Cl_2. Release of the ligands from the resin is complete within 30 minutes, as evidenced by MAS NMR of the residual resin. As is apparent from Table I the coupling is general and highly efficient.[11] While cleavage from the resin is facile, the linkage is sufficiently stable to carry out the wide range of chemistry commonly used in small molecule library construction. Some illustrative examples carried out in our laboratories are shown in scheme III.



Scheme III

In summary, Rink-chloride resin is a versatile support which allows release of amides, sulfonamides, amines, thiols, alcohols or carboxylic acids under mild acid conditions. It should find

wide application in solid phase synthesis and we are currently using the Rink-chloride resin in the construction of several organic small molecule libraries.

Acknowledgement: I thank Drs. Jerry L. Adams and Micheal L. Moore for helpful discussions and encouragement.

References and Notes

1. (a) Thompson, L. A.; Ellman, J. A.*Chem. Rev.* **1996**, *96*, 555-600. (b) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steel, J. *Tetrahedron* **1995**, 51, 8135-8173. (c) Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A., Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (d) Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385. (e) Ecker, D. J.; Crooke, S. T. *Biotechnology* **1995**, *13*, 351.
2. Rink, H., *Tetrahedron Lett.* **1987**, *28*, 3787-3790.
3.(a) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem.* **1996**, *61*, 924-928 (b) Norman, T. C.; Gray, N. S.; Koh, J. T.; Schultz, P. G. *J. Am. Chem. Soc.* **1996**, *118*, 7430-7431 (c) Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993-6996. Zhang, H-C; Brumfield, K. K.; Maryanoff, B. E. *Tetrahedron Lett.* **1997**, *38*, 2439
4. A recent report describes preparing sulfonamides on the Rink resin: Beaver, K. A.; Siegmund, A. C.; Spear, K. L. *Tetrahedron Lett.*, **1996**, *37*, 1145-1148.
5. Purchased from Novabiochem.
6. Chlorine analysis and MAS NMR[10] indicate completion of reaction.
7. Use of carbon tetrachloride as the chlorine source afforded incomplete conversion.
8. To a suspension of the resin **1** (0.2g., 0.13 mmol.) in THF (4 mL) was added triphenylphosphine (0.187g, 0.715mmol.) and hexachloroethane (0.169 g., 0.715 mmol.) and the mixture was agitated by shaking under argon for 6h. The resin was filtered and washed with THF and was used in the next step. MAS NMR[10] of the product clearly indicates the disapperance of the -CH(OH) signal at 5.88 ppm.
9. To a suspension of the Rink-chloride (1.0g, 0.52 mmol) in dichloroethane (5mL) was added Hünig's base (0.3mL) and 3-4-dimethoxyphenethyl amine (0.5mL, 1.7mmol.). The mixture was agitated in a shaker, under a blanket of argon for 24h. The resin was filtered and washed with CH_2Cl_2 and methanol. Elemental analysis and MAS NMR[10] indicate completion of the reaction.
10. (a) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588-7590. (b) Garigipati, R. S.; Adams, B.; Adams, J. L.; Sarkar, S. K. *J. Org. Chem.* **1996**, 61,2911-1914.
11. The purity was determined by HPLC and MS and hence refers to the %purity of the crude material.

(*Received in USA* 12 *May* 1997; *revised* 28 *July* 1997; *accepted* 1 *August* 1997)