

[B0002]

Trapping of Nucleophiles by Rink Resin

by **Wolfgang K.-D. Brill**

Novartis Pharma Inc. R-1060.3.42, CH4002 Basle, Switzerland;

E-mail: wolfgang_k-d.brill@pharma.novartis.com

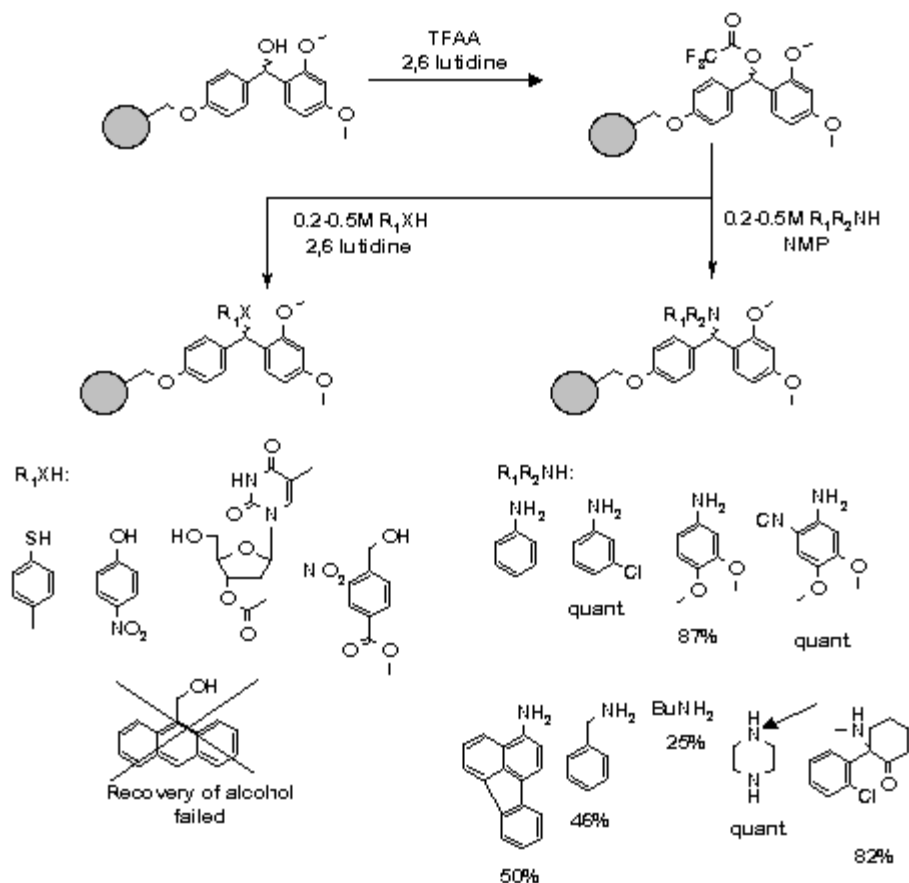
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Commonly, molecules synthesized on a solid support are attached to the solid phase by a linker entity, often an acid labile linker. A commonly used acid labile linker is the "Rink-linker"¹ which provides solid phase attachment via an amide or an ester bond. Upon acid treatment target molecules are released, which all bear a "trace of the linker", such as an acid or primary amide functionality. Here, we describe a method to constitute a much wider variety of molecules by trapping a "Rink-cation" with a number of alcohols, amines or thiols.

Formation of the cation upon TFA-treatment of an Fmoc-urethane was more facile than that from "Rink"-amine resin. However partial degradation of the linker, such as demethylation during the acid treatment might cause unwanted side reactions during subsequent synthetic steps.

To avoid this problem, we also attempted to synthesize the "Rink"-trifluoroacetate under basic conditions.

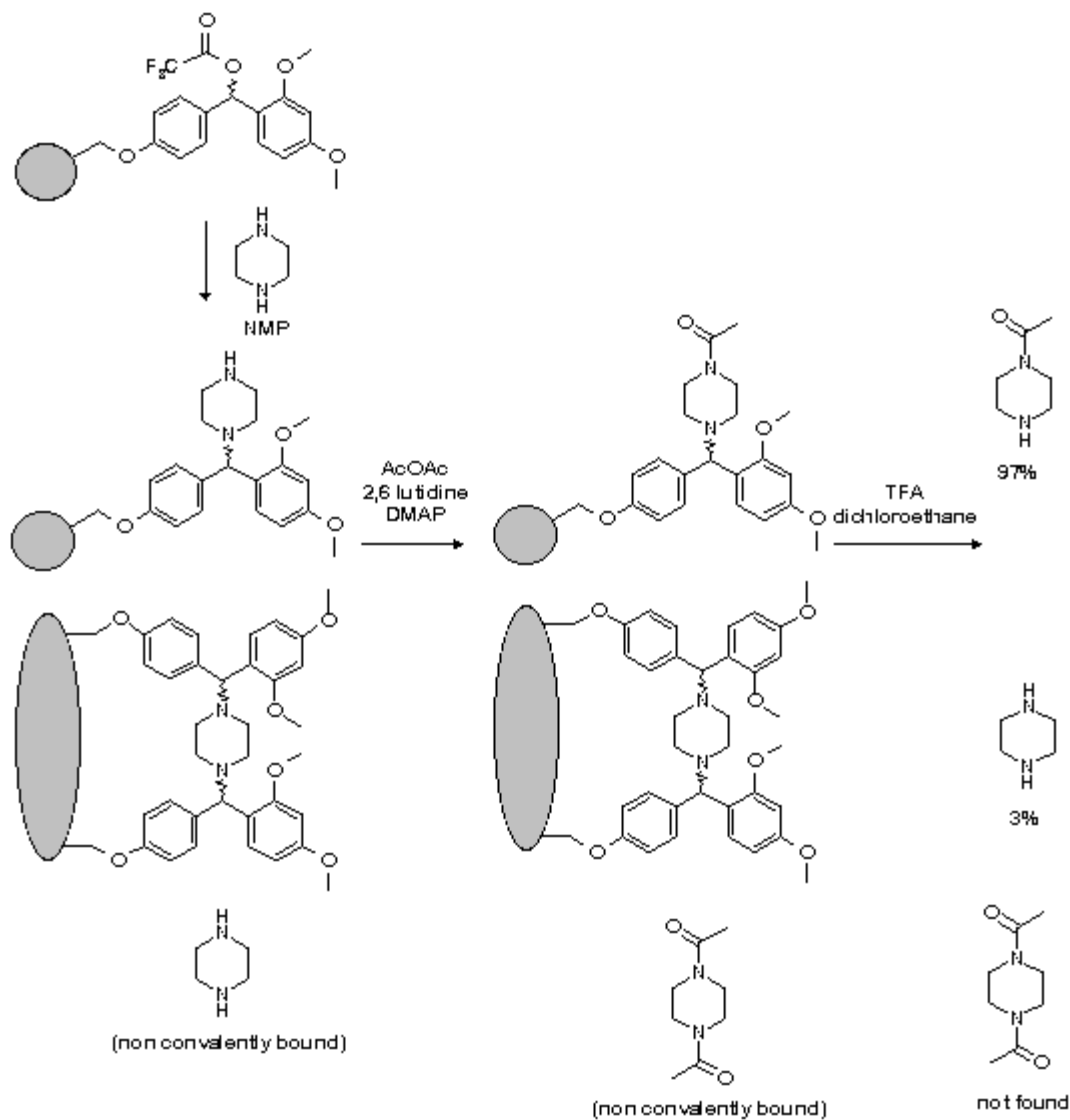
Figure 1:



All reactions were carried out on polystyrene beads ("Rink acid resin", Fluka) Yields are based on the recovered nucleophile after treatment with 20% TFA in $\text{ClCH}_2\text{CH}_2\text{Cl}$. The amines were recovered as TFA-salts, the alcohols partially as esters with TFA. Thiokresol was liberated from the resin by 62h treatment with 95%TFA/ H_2O .

Thus, treatment of Rink-OH resin with TFAA in 2,6-lutidine gave a pale yellow resin, indicative for mainly covalently bound trifluoroacetate. These covalent polymeric trifluoroacetates can be displaced with a series of nucleophiles, namely alcohols amines and thiols (Figure1). In case of piperazine, exhaustive acylation was performed after the immobilization using acetic anhydride/DMAP (Figure 2).

Figure 2:



The fact that monoacylated piperazine was recovered as main product after the TFA cleavage indicated a covalent attachment of piperazine via one of its nitrogens. The 3% unacylated piperazine also isolated might point to either incomplete acylation or to at least 3% crosslinking during the immobilization.

Literature: H. Rink, *Tetrahedron Lett.* 3787(1987)

Comments

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