Polymeric De-blocking Agents for the Fluoren-9-ylmethoxycarbonyl (FMOC) Amino-protecting Group

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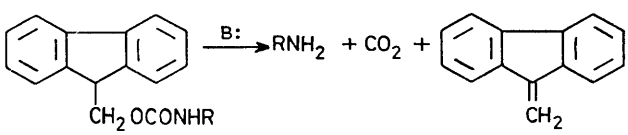
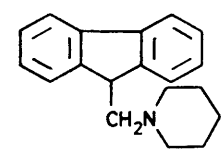
Summary The fluoren-9-ylmethoxycarbonyl (FMOC) amino-protecting group can be de-blocked at room temperature by means of an insoluble polymeric reagent incorporating cyclic secondary amino-functions.

SOMETIME ago we described a new amino-protecting group which was de-blocked by means of ordinary amines such as liquid ammonia, ethanolamine, morpholine, piperidine, *etc.* at room temperature or below.[1] When a cyclic secondary amine such as piperidine is used, the by-product in the de-blocking process, dibenzofulvene (**2**), reacts with an excess of cyclic amine to give the adduct (**3**). Formation of adducts such as (**3**) is characteristic only of cyclic secondary amines. Morpholine and piperazine give adducts but ethanolamine and diethylamine do not. It is sometimes difficult to separate the desired amine, RNH_2, from the adduct (**3**) and in order to avoid these separation problems we have introduced a cyclic secondary amino-function on to an insoluble cross-linked polystyrene and have used the resulting polymeric organic reagent[2] to provide a mild de-blocking system. For convenience of attachment to the polymeric matrix, the bifunctional molecule piperazine was used to attach the desired unit to the resin. Treatment of



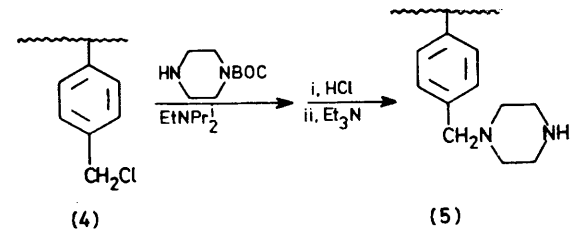
(1) (2)



(3)

chloromethylated polystyrene (**4**) [3·5 mequiv. Cl per g of resin, 1% divinylbenzene (DVB)] with the monofunctional t-butoxycarbonyl (BOC) derivative of piperazine followed by acidic removal of the BOC group gave the piperazine polymer (**5**) containing 2·4 mequiv. of active NH units per gram of polymer.

Upon suspending 6—10 mol. equiv. of polymer (**5**) in a methylene dichloride solution of (**1**; R = *p*-ClC_6H_4) and stirring for 12—24 h the resulting amine (*p*-$ClC_6H_4NH_2$, 80—97%) could be isolated simply by filtration of the polymer and evaporation of the solvent. All dibenzofulvene liberated was scavenged by the insoluble polymer. When the piperazine polymer (**5**) was prepared from a macroreticular polystyrene (Rohm and Haas XE-305), the scavenging reaction was more sluggish although the presence of more polar solvents catalysed the addition reaction. For example, in the presence of methanol or formamide, addition of dibenzofulvene took place rapidly with the macroreticular resin. If the FMOC derivative is one which gives a product insoluble in methylene dichloride but soluble in water, the de-blocking reaction can be carried out by the addition of a small amount of water to the system to prevent precipitation of the product on the polymer. By this technique the FMOC derivative of tryptophan gave a 90% yield of the pure amino-acid.



(**4**) (**5**)

A sample of the piperazine polymer (**5**) (2·4 mequiv. NH per g, 1% DVB) which had been completely saturated by dibenzofulvene units by reaction with excess of the urethane (**1**) was treated at room temperature for 12 h with n-butyllithium in tetrahydrofuran. After filtration and washing with dioxan and water this regenerated piperazine polymer could be re-used in the deblocking–scavenging process with the urethane (**1**; R = *p*-ClC_6H_4) to give *p*-chloroaniline uncontaminated by dibenzofulvene.

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[1] L. A. Carpino and G. Y. Han, *J. Amer. Chem. Soc.*, 1970, **92**, 5748; *J. Org. Chem.*, 1972, **37**, 3404; 1973, **38**, 4218.

[2] For recent reviews on the advantageous utilization of polymeric organic reagents, see: J. I. Crowley and H. Rapoport, *Accounts Chem. Res.*, 1976, **9**, 135; A. Patchornik, *Pure Appl. Chem.*, 1975, **43**, 503; C. C. Leznoff, *Chem. Soc. Rev.*, 1974, **3**, 65; C. G. Overberger and K. N. Sannes, *Angew. Chem. Internat. Edn.*, 1974, **13**, 159.