



An improved two-resin method for the cleavage of tertiary amines from REM resin

Carolina Alhambra,^a Julia Castro,^b Jose Luis Chiara,^{a,*} Esther Fernández,^b
Alfonso Fernández-Mayoralas,^a José M. Fiandor,^b Silvestre García-Ochoa^{b,*} and
María D. Martín-Ortega^{a,†}

^a*Instituto de Química Orgánica, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain*

^b*GlaxoSmithKline S.A., P.T.M., Severo Ochoa, 2, E-28760 Tres Cantos, Madrid, Spain*

Received 18 June 2001; revised 24 July 2001; accepted 25 July 2001

Abstract—The use of polymer-bound guanidine **6b** or polymer-bound phosphazene **6c** significantly improve the yield of the Hofmann elimination step in the preparation of tertiary amines using REM resin, providing products with superior purities and free from contamination with trialkylammonium salts. © 2001 Elsevier Science Ltd. All rights reserved.

The parallel synthesis of small amounts of discrete compounds using solid-phase synthesis techniques is one of the prime current strategies for lead discovery and lead optimization in the pharmaceutical industry.¹ In this context, the development of new methods for the traceless tethering of compounds to polymer supports is of considerable interest.² Additionally, the use of recyclable resins can improve the cost effectiveness of large scale solid-phase organic synthesis by allowing the preparation of multigram amounts of product by repeated synthesis. One such resin, the REM resin (**1**),³ is based on an acrylic ester traceless linker useful for the synthesis of tertiary amines. Initial Michael addition of a primary amine to **1**, followed by reductive *N*-alkylation, quaternization with alkyl halide, and subsequent Hofmann elimination (Scheme 1) releases the product tertiary amine (**5**), regenerating the resin linker. In the original reports on this approach,³ the required Hofmann cleavage was promoted under mild conditions by overnight treatment with an excess of a soluble base (Et₃N or DIEA). However, under these conditions, the released tertiary amine was usually contaminated with Et₃N or DIEA hydrobromide or hydroiodide salts. Initially, this problem was circumvented by post-cleavage purification using time-consuming aqueous extraction or SPE chromatography. This creates a serious

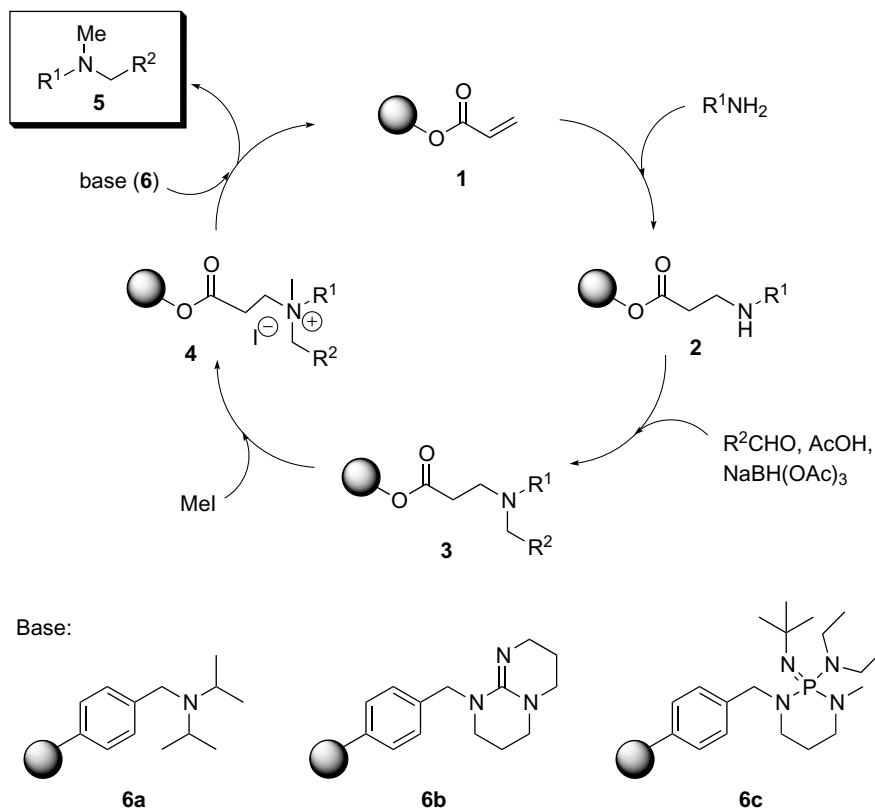
manipulation problem when making medium/large chemical libraries (>1000 compounds). More recently, a number of improved cleavage procedures have been developed using either weakly basic Amberlite resin,^{4a} a solid-supported piperazine,^{4b} gaseous ammonia,⁵ or a soluble polymer-bound tertiary amine.⁶ In the case of the two-resin system,⁴ the supported base acts simply as a regenerating agent for the soluble tertiary amine which is, in fact, the base that promotes the Hofmann elimination.

In the context of a program directed toward the preparation of large libraries of compounds containing a tertiary amine moiety following this approach (Scheme 1), we selected the convenient two-resin cleavage method reported by Murphy,^{4a} even though this would prevent recycling of the REM resin at the end of the synthesis due to mixing with the second resin. A supported tertiary amine, resin **6a**,⁷ was chosen initially for this purpose. However, the yield of the Hofmann elimination step was only modest in most cases, with acceptable final purities (>80%), as shown by ¹H NMR analysis of the crude released products.

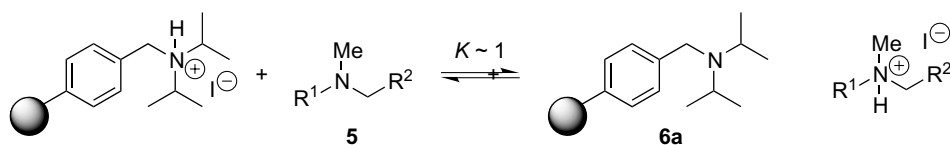
In an effort to increase the cleavage yields and purity standards, we decided to test other supported bases. We realized that, after Hofmann elimination, a chemical equilibrium would be attained between the hydroiodide salts of the added supported base and the soluble amine product (Scheme 2). Since both bases are tertiary amines, the equilibrium constant for this acid–base process would not be far from 1. This means that, for

* Corresponding authors. Tel.: +34-915622900; fax: +34-915644853 (J.L.C.); tel.: +34-918070616; fax: +34-918070550 (S.G.O.); e-mail: jl.chiara@iqog.csic.es; sgo6741@glaxowellcome.co.uk

† Present address: Lilly, S.A., Avenida de la Industria, 30, E-28108 Alcobendas, Madrid, Spain.



Scheme 1.



Scheme 2.

a threefold mole excess of supported base added, up to ca. 25% of the released tertiary amine product would be in the form of its hydroiodide salt. Besides, this partial protonation of the soluble base would compromise the Hofmann elimination step (see above). An obvious solution to this problem could be either to use a very large excess of supported base or, more conveniently, a stronger supported base. Two such bases, a polymer-bound guanidine (**6b**)⁸ and a polymer-bound phosphazene (**6c**)⁹ were tried (Scheme 1). As a hint to the relative base strengths of **6a–c**, Fig. 1 shows the pK_a values reported for their corresponding non-supported analogs.^{10,11}

To test the proposed methodology, a small library of 15 tertiary amines was constructed following Scheme 1.¹² Table 1 shows the results obtained using **6a–c** for this test library. To our delight, greatly improved yields were achieved when **6b** was used, and an even greater efficiency was seen in the case of **6c**. Thus, a clear correlation between yield and base strength was observed, as anticipated. In two cases, negligible product amounts (<2%) were obtained using **6a**, but up to 30% product was released when **6c** was added (see

Table 1). Moreover, the purity of the released tertiary amines also improved significantly to >90% when **6b** or **6c** were used, as shown by HPLC and ¹H NMR analysis of the crude samples. In general, although the yields were somewhat lower, **6b** gave slightly higher purities than **6c**.¹³

In conclusion, we have shown that the use of the strong supported bases **6b** and **6c** can significantly improve the yield of the Hofmann elimination step in the preparation of tertiary amines using REM resin, providing products with superior purities and free from contamination with trialkylammonium salts.

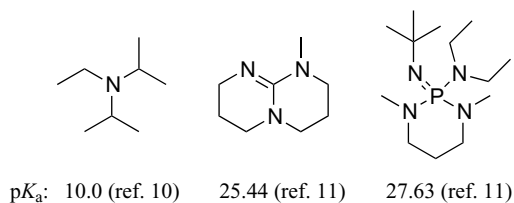
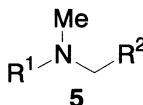
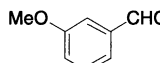
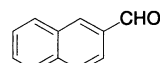
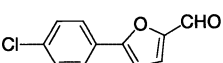
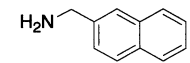
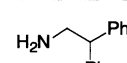
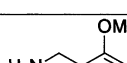
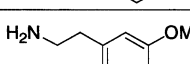
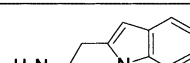


Figure 1.

Table 1. Yields of crude tertiary amines (**5**) produced via Scheme 1 using three different supported bases (**6a–c**) to promote the Hofmann elimination^a

 5		R²CHO								
										
Supported Base		6a	6b	6c	6a	6b	6c	6a	6b	6c
R¹NH₂		<2	19	28	20	24	33	12	69	80
		2	30	37	10	50	51	24	83	97
		8	93	94	18	62	97	28	97	97
		20	77	97	29	97	97	33	97	97
		<2	14	30	3	24	25	10	73	97

^a Yields correspond to the whole synthetic process and have been determined by dissolving crude **5** in 0.75 mL of a 5 mM solution of HMDS, as internal standard, in CDCl₃ and comparing the ¹H NMR integrals of the sample signals to that of the internal standard, as described in Ref. 14. Calculations are based on the initial loading of the Wang resin used to prepare **1**.

References

- (a) *Combinatorial Chemistry and Technology. Principles, Methods and Applications*; Miertus, S.; Fassina, G., Ed.; Marcel Dekker: New York, 1999; (b) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; Wiley-Interscience: New York, 2000.
- (a) James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946; (b) Bräse, S.; Dahmen, S. *Chem. Eur. J.* **2000**, *6*, 1899–1905; (c) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2158; (d) Comely, A. C.; Gibson, S. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1012–1032.
- (a) Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3209–3212; (b) Brown, A. R.; Rees, D. C.; Rankovic, Z.; Morphy, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 3288–3295; (c) Luo, Y.; Ouyang, X.; Armstrong, R. W.; Murphy, M. M. *J. Org. Chem.* **1998**, *63*, 8719–8722; (d) Cottney, J.; Rankovic, Z.; Morphy, J. R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1323–1328; (e) Plater, M. J.; Murdoch, A. M.; Morphy, J. R.; Rankovic, Z.; Rees, D. C. *J. Comb. Chem.* **2000**, *2*, 508–512.
- (a) Ouyang, X.; Armstrong, R. W.; Murphy, M. M. *J. Org. Chem.* **1998**, *63*, 1027–1032; (b) Yamamoto, Y.; Tanabe, K.; Okonogi, T. *Chem. Lett.* **1999**, 103–104.
- Brown, A. R. *J. Comb. Chem.* **1999**, *1*, 283–285.
- Toy, P. H.; Reger, T. S.; Janda, K. D. *Org. Lett.* **2000**, *2*, 2205–2207.
- PS-DIEA (1% DVB cross-linked polystyrene; loading: 3–4 mmol/g) was purchased from Argonaut Technologies.
- 1,5,7-Triazabicyclo[4.4.0]dec-5-ene on 2% DVB cross-linked polystyrene (loading: ~2.6 mmol/g) was purchased from Fluka.
- 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on 2% cross-linked polystyrene (loading: ~2.3 mmol/g) was purchased from Fluka.
- Measured in THF at 20°C. Nurminen, E. J.; Mattinen, J. K.; Loennberg, H. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2551–2556.
- Measured in MeCN at 25°C. Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435–2454.
- Experimental procedure: REM resin **1** (prepared from Wang resin, Rapp Polymer; loading 0.8–0.9 mmol/g), was treated with a 1 M solution of R¹NH₂ (10 mol excess) in DMF and the mixture was stirred in an orbital shaker for 72 h. The resin was filtered, thoroughly washed with DMF (3×), DCM (3×), THF (3×), DCM (3×) and Et₂O (2×), and dried under vacuum to give **2**. To 90 mg of resin-bound amine (**2**) was added 1.8 mL of a 1 M solution of R²CHO in DMF containing 5% AcOH. After stirring at rt for 1 h in an orbital shaker, NaBH(OAc)₃ (381 mg, 1.8 mmol) was added and stirring was continued for 20 h. The resin was filtered, washed with MeOH (5×), DCM (3×), DMF (3×), DCM (3×) and DMF (3×) to give **3**. To this resin sample was added a 1 M solution of MeI in DMF (1.8 mL) and the mixture was stirred at rt in an orbital shaker for 48 h. The resin was filtered, washed with DMF (5×), DCM (3×), THF (3×), DCM (3×) and Et₂O (2×) and dried overnight under vacuum to give the

solid-supported tetralkylammonium salt **4**. Resin sample **4** was divided into three parts and each treated with a 3 mol excess of a different supported base **6a–c** in 0.5 mL of THF. After stirring in an orbital shaker at rt for 24 h, the mixture was filtered, and the resin was washed with CH₂Cl₂ (2×0.2 mL) and MeOH (2×0.2 mL). The filtrate and washings combined were evapo-

rated at reduced pressure to give the crude tertiary amine **5**.

13. When **6c** was used, two unassigned small multiplets at 1.82 and 3.17 ppm are always observed in the ¹H NMR spectra of the crude tertiary amine.
14. Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, G. R.; Cortez, E. *J. Org. Chem.* **1998**, *63*, 708.