Pergamon

Tetrahedron Letters 42 (2001) 5579–5581

TETRAHEDRON LETTERS

Pyrrolidine synthesis on polystyrene supports: development of a 'one-pot' dipolar cycloaddition strategy

Anthony G. M. Barrett,[a,*] Raymond J. Boffey,[a] Mathias U. Frederiksen,[a] Christopher G. Newton[b] and Richard S. Roberts[a]

[a]*Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, UK*
[b]*Aventis Pharma, Dagenham Research Centre, Rainham Road South, Dagenham, Essex RM10 7XS, UK*

Received 3 May 2001; accepted 14 June 2001

Abstract—Preparation of substituted pyrrolidines was achieved by solid-phase synthesis via a room temperature 1,3-dipolar cycloaddition of a silver-azomethine ylide, generated in situ, with a polymer-supported maleimide.

Combinatorial chemistry offers the potential to generate highly diverse, non-peptidic compounds and thus, aid the discovery of biologically active compounds.[1,2] The continual development of lead compounds for both the pharmaceutical and agrochemical industries requires the generation of novel libraries. Thus, it is essential to develop reliable chemistry, which allows the synthesis of highly functionalized and diverse compounds around a particular scaffold. Recently we had occasion to examine the synthesis of the bicyclic imides **1** (Fig. 1). We envisaged the formation of the pyrrolidine portion of the molecule through a [3+2] dipolar cycloaddition[3] between a polymer-supported maleimide **3** and the azomethine ylide (formed by condensation of an α-amino acid methyl ester **4** and an aldehyde **5**).

Libraries of pyrrolidines have been synthesized via three-component cycloaddition with the point of attachment to the resin being either the aldehyde,[4] the acid of the amino acid group[5,6] or the dipolarophile.[7]

For the synthesis of compounds **1**, we especially wanted the imide entity to be an *N*-unsubstituted succinimide unit since maleimide can be considered as a bioisostere of uracil.[8] In general and in contrast with *N*-alkyl and *N*-aryl maleimides,[9] maleimide itself is unsuitable as a dipolarophile in [3+2] cycloaddition reactions on account of competing reactions such as the addition of the imide nitrogen to the azomethine C=N bond.[10] Cycloaddition using *N*-carbamoylmaleimide followed by acidic cleavage of the carbamoyl group has been described, although with limited success.[6] Therefore, we sought to develop a *N*-resin-bound maleimide equivalent.

We were able to load silver maleimide on trityl chloride resin[11,†] and to carry out the Diels–Alder reaction with cyclopentadiene. Cleavage using 50% TFA–CH_2Cl_2 gave imide **8** in 33% yield (based upon the commercial trityl resin loading) and >95% purity by LCMS[‡]

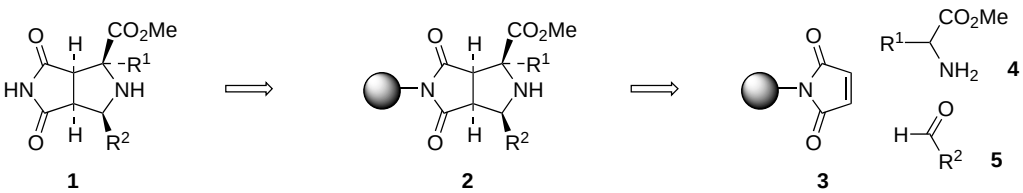


Figure 1.

Keywords: cycloaddition; maleimide; solid support; trityl resin.

* Corresponding author. E-mail: agmb@ic.ac.uk

† Trityl chloride resin (1% divinylbenzene crosslinked, 1.1 mmol g^{-1} loading, 100–200 mesh) was supplied by Fluka. Resin **7** was characterized by FT-IR.

‡ Analysis was performed using a C-18, reverse phase column, 0.1% aqueous formic acid-methanol gradient. Detection was by simultaneous UV (Gilson 119 detector, 220 nm) and light scattering detection (Sedex 65). Mass spectra were recorded continually on a Fisons VG platform II electrospray.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01061-9

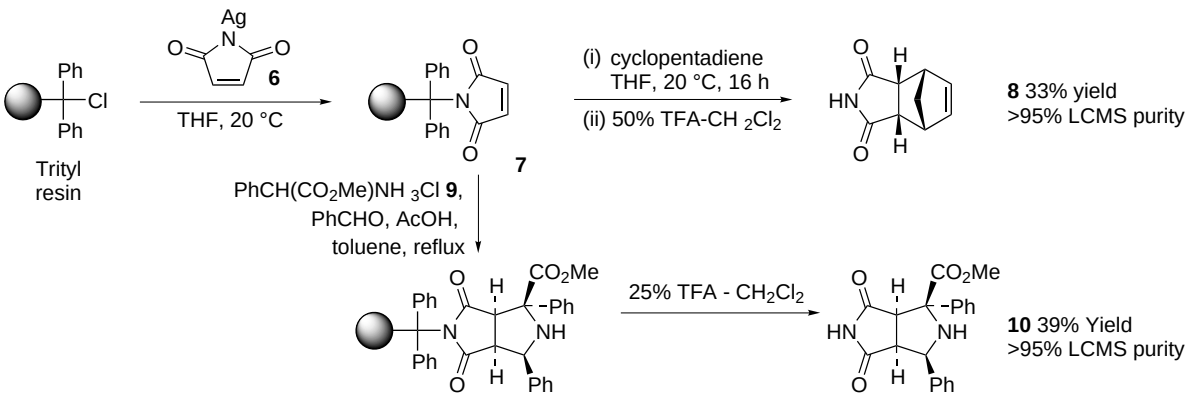
(Scheme 1). Next, we reacted resin **7** with excess hydrochloride **9**, benzaldehyde and acetic acid in toluene at reflux. Cleavage of the product from the resin with 25% TFA–CH_2Cl_2 gave the desired pyrrolidine compound **10** in 39% overall yield (>95% purity by LCMS)-(Scheme 1).[§]

Although these results were encouraging, this method would preclude the use of aldehydes containing α-hydrogens, due to the predominance of the unreactive enamine tautomer **11** in the mixture (Fig. 2).

We found a solution to this problem by performing the imine (e.g. **13**) in solution and using a silver acetate stabilized azomethine ylide in non-polar solvent at room temperature, as developed by Grigg and co-workers.[12] Cleavage from the resin with 50% TFA–CH_2Cl_2 gave the imide **14** (36% yield, >95% pure by LCMS) (Scheme 2). Although this method gave a pure product, in the context of a library we would have had to preform the imine for every combination of amino acid **4** and aldehyde **5** in solution.

When we tried a 'one-pot' procedure by combining all of the reactants together, we isolated no product presumably due to the incompatibility of the amine hydrochloride and the silver acetate, generating silver chloride. We finally succeeded in our 'one-pot' synthesis by combining the preformed free base of the amino acid ester **4**, the aldehyde **5**, the dehydrating agent ($MgSO_4$), the Lewis acid (AgOAc), the base (NEt_3) and the dipolarophile (maleimide resin **7**) in toluene and shaking the slurry for 3 days. The resin was washed thoroughly with toluene, THF, water, DMSO, dichloromethane and methanol and cleaved with 50% TFA–CH_2Cl_2 to give the desired bicyclic imides **1** (Scheme 3). HPLC purities of a 120 member library showed 73 compounds with a purity >70%. However, in spite of the extensive washing procedure, the desired products were invariably contaminated with metal salts. Flash chromatography of random library members (Scheme 3) gave high purity samples and their structures were confirmed by ^{1}H NMR, ^{13}C NMR, IR, and HRMS.

In conclusion, we have developed methods for the resin capture of azomethine ylides using a resin-bound maleimide and the subsequent cleavage both for individual compounds in moderate yield and excellent purities and generation of libraries for lead discovery.[13]



Scheme 1.

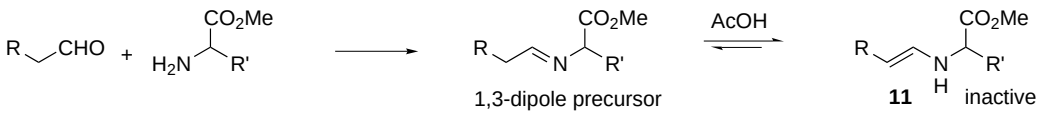
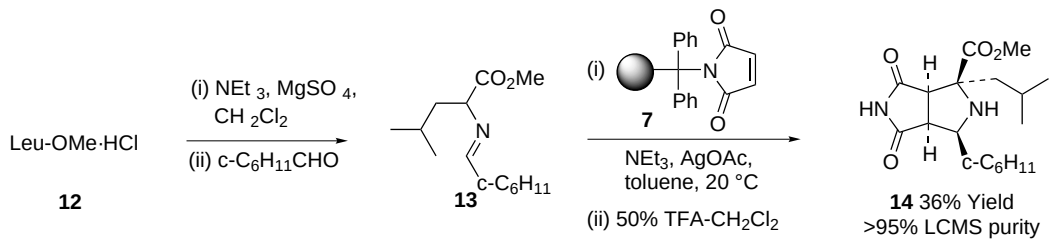
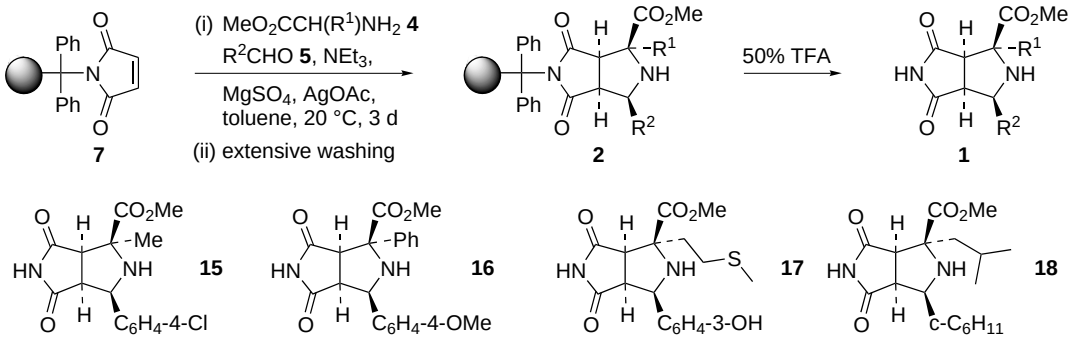


Figure 2.



Scheme 2.

[§] The relative stereochemistry of **10** was assigned by analogy with the X-ray crystal structure of the product derived (in solution, 92% yield) using *N*-benzylmaleimide as the dipolarophile.



Scheme 3.

Acknowledgements

We thank Aventis Pharma for the most generous support of our programmes on parallel and combinatorial syntheses (to R.J.B and R.S.R.) under the auspices of the TeknoMed project and the Norwegian Research Council (M.U.F) for predoctoral fellowship support. In addition we thank GlaxoSmithKline for their endowment (to A.G.M.B.) and the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College.

References

1. (a) Hermkens, P. H. H.; Ottenheijm, H. J. C.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527; (b) Hermkens, P. H. H.; Ottenheijm, H. J. C.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643; (c) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. J. C.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385; (d) Dolle, R. E.; Nelson, Jr., K. H. *J. Comb. Chem.* **1999**, *1*, 235.
2. (a) Watson, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1903; (b) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859.
3. Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89.
4. Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671.
5. (a) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 3081; (b) Bicknell, A. J.; Hird, N. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2441; (c) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029; (d) Maclean, D.; Schullek, J. R.; Murphy, M. M.; Ni, Z.-J.; Gordon, E. M.; Gallop, M. A. *Proc. Natl. Acad. Sci., USA* **1997**, *94*, 2805; (e) Costero, A. M.; Pitarch, M.; Cano, M. L. *J. Chem. Res. (S)* **1994**, 316.
6. Henkel, B.; Stenzel, W.; Schotten, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 975.
7. Hollinshead, S. P. *Tetrahedron Lett.* **1996**, *37*, 9157.
8. Mumper, M. W.; Aurenge, C.; Hosmane, R. S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2847.
9. For example, see: Aly, M. F.; Younes, M. I.; Metwally, S. A. M. *Tetrahedron* **1994**, *50*, 3159.
10. Peyronel, J.-F.; Grisoni, S.; Carboni, B.; Courgeon, T.; Carrié, R. *Tetrahedron* **1994**, *50*, 189.
11. Schwartz, A. L.; Lerner, L. M. *J. Org. Chem.* **1974**, *39*, 21.
12. Grigg, R.; Montgomery, J.; Somasunderam, A. *Tetrahedron* **1992**, *48*, 10431.
13. **Typical procedure:** Alanine methyl ester (92 mg, 0.66 mmol) in toluene (2 mL) was added to a slurry of maleimide resin (**7**) (200 mg, ca. 0.22 mmol), AgOAc (110 mg, 0.66 mmol), $MgSO_4$ (100 mg, 0.66 mmol), NEt_3 (0.11 mL, 0.78 mmol), 4-chlorobenzaldehyde (93 mg, 0.66 mmol) and toluene (3 mL). The resultant suspension was agitated at ambient temperature (56 h), whereupon it was filtered and washed sequentially with toluene, THF, DMSO, water, THF, CH_2Cl_2 and methanol and dried in vacuo. The bicyclic succinimide resin (i.e. **2**) was added to a solution of 50% TFA–CH_2Cl_2 (10 mL) and agitated for 4 h. The resin was filtered, and washed with CH_2Cl_2 and methanol. The filtrate was concentrated, then dissolved in acetone and filtered through a small pad of Celite and the resultant filtrate was concentrated in vacuo to reveal essentially pure desired bicyclic imide **15**. Flash column chromatography (1:1 EtOAc:hexane) afforded analytically pure product: ^{1}H NMR (300 MHz, $CDCl_3$) 8.11 (bs, 1H), 7.34 (s, 4H), 4.76 (dd, 1H, $J=8.0$, 6.5), 3.87 (s, 3H), 3.54 (dd, 1H, $J=8.0$, 7.5), 3.34 (d, 1H, $J=7.5$), 2.52 (d, 1H, $J=6.5$), 1.61 (s, 3H); HRMS (CI) calcd for $C_{15}H_{16}ClN_2O_4$; 323.0799; found 323.0797.