

# The 4-azidobenzoyloxycarbonyl function; application as a novel protecting group and potential prodrug modification for amines

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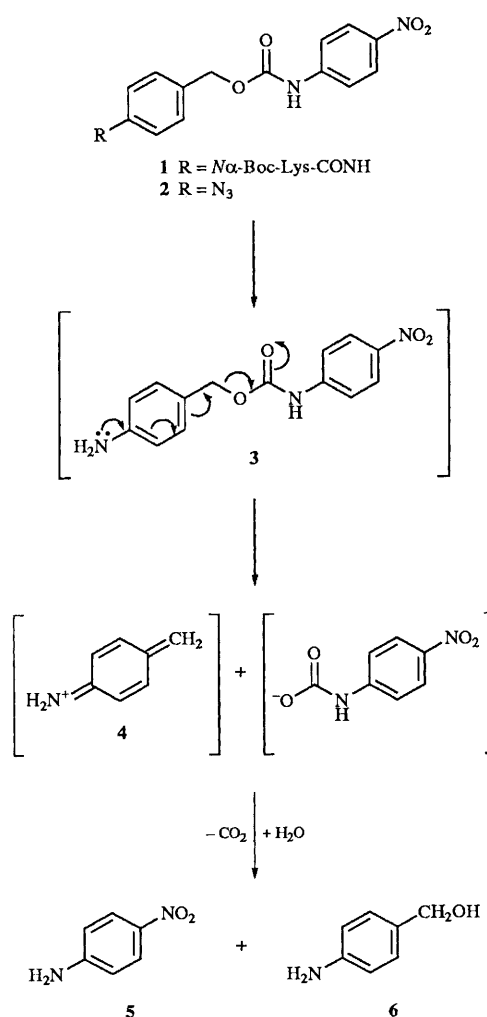
A series of 4-azidobenzylcarbamates [4-N<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub>-O-CO-N(H)-C<sub>6</sub>H<sub>4</sub>-X; X = H, Me, MeO, Br, Cl, NO<sub>2</sub>] have been prepared in good yield, and in high purity, by reaction of 4-azidobenzyl alcohol with the corresponding aryl isocyanate, or by displacement of 4-nitrophenol from 4-azidobenzyl-4-nitrophenyl-carbonate by the appropriate amine. The 4-azidobenzylcarbamates were shown to undergo rapid reduction in the presence of dithiothreitol, and the resultant 4-aminobenzylcarbamates underwent immediate cascade degradation to release the target amine. The mild conditions used in this conversion may prove useful in the protection of amines during synthetic procedures or as a possible mode of bioactivation of prodrugs.

## Introduction

Although the synthetic utility of the azido group is well established,<sup>1</sup> the biological importance of this substituent has only recently gained recognition,<sup>2</sup> owing largely to the emergence of antiviral azido-substituted nucleosides. Azides are readily reduced to their corresponding amines by a diverse range of reagents,<sup>3</sup> and bioreduction also appears to represent the principal metabolic fate of the azido group in organic azides including 3'-azido-3'-deoxythymidine (AZT).<sup>4</sup> Analogous studies in our laboratories with the lipophilic antifolate *m*-azidopyrimethamine,<sup>5,6</sup> and a series of simple aryl azides,<sup>7</sup> have also demonstrated the enzyme-catalysed reduction of azides *in vitro*. Azides are readily converted into amines by thiols under mild reaction conditions, with dithiols proving particularly effective,<sup>8</sup> and reduction by endogenous thiols may also contribute to the biotransformation of azides. Reduction of aryl azides by the abundant endogenous monothiol glutathione has, in fact, been demonstrated, albeit at a greatly reduced rate compared with dithiols.<sup>9,10</sup>

We have previously studied the utility of the azide moiety in the design of antifolates<sup>11</sup> and anti-inflammatory agents<sup>12,13</sup> for topical delivery, where this group proved to be a useful probe for quantitative studies of dermal penetration using attenuated total reflection FT-IR spectroscopy.<sup>14</sup> As part of continuing studies to establish aromatic azides as lipophilic precursors of arylamines, with application in drug design,<sup>2,5</sup> we have investigated 4-azidobenzyl carbamates as potential tripartite prodrugs. Carl *et al.*, have reported that treatment of the model tripartite prodrug system **1** with trypsin resulted in rapid release of 4-nitroaniline **5** and 4-aminobenzyl alcohol **6**, and proposed a mechanism whereby enzyme-catalysed conversion of the 4-amido group of **1** to the corresponding arylamine **3** evoked spontaneous fragmentation *via* the intermediacy of the iminoquinone **4** (Scheme 1).<sup>15</sup>

Decomposition of **3** was attributed to the generation of the electron-donating arylamino substituent which facilitates solvolytic cleavage of the benzyl carbamate. Aromatic amido-



**Scheme 1** Putative mechanism for the reduction-fragmentation of amido- and azido-benzylcarbamate tripartite prodrugs

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and azido-substituents exhibit very similar electronic properties ( $\sigma_p = 0.00$  and  $0.15$ , respectively), both being substantially less electron-donating than an amino group ( $\sigma_p^+ = -0.66$ ).<sup>16</sup>

implying that the 4-azidobenzyl carbamate derivative **2** will also be stable. However, chemical or enzyme-catalysed reduction of the azide should afford **3**, with subsequent fragmentation liberating 4-nitroaniline **5** and 4-aminobenzyl alcohol **6** in a manner analogous to that observed for **1**. Hence, **2** may be regarded as an alternative model for a tripartite prodrug where the azido substituent represents the specifier group, the benzyloxycarbonyl moiety the linker and 4-nitroaniline the amine drug. Also, since azide reduction may be effected under very mild conditions by a variety of reductants, the 4-azidobenzyl carbamate (ACBZ) group also represents a potentially useful protecting group for amines, analogous to the benzyloxycarbonyl (CBZ) group, but selectively removable in the presence of this and other amine-protecting groups. Indeed, we have shown previously that this activated urethane may prove of benefit as a readily removable protective group<sup>17</sup> or as the basis for the bioactivation of soft drugs of antiviral phosphates.<sup>18</sup> The 4-azidobenzyl and 4-azidomethyleneoxybenzyloxycarbonyl group have both been reported previously as protecting functions for hydroxy<sup>19</sup> and amino<sup>20</sup> substituents, respectively, but each requires two-step vigorous reaction conditions to effect deprotection.

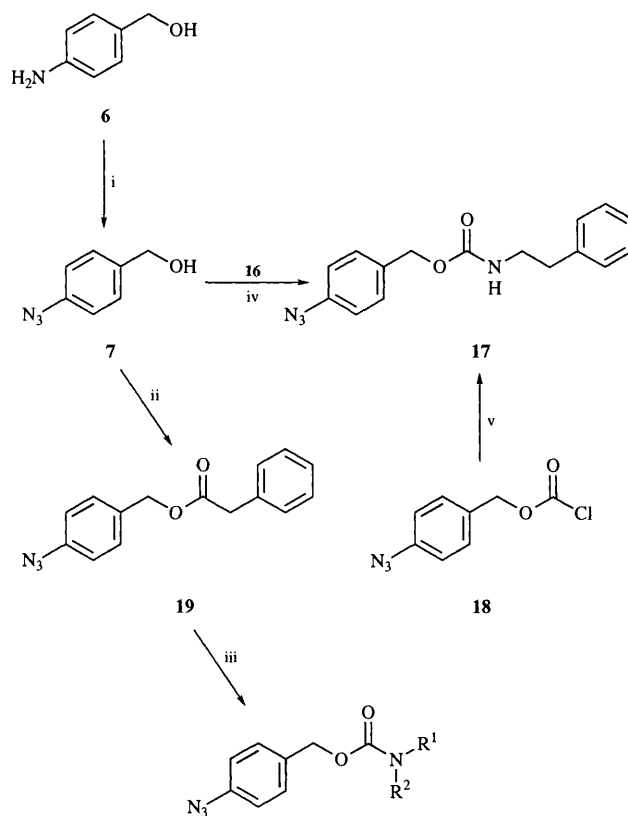
In this paper, we describe the synthesis of a series of azidobenzyl carbamates and the results of studies with the 4-azidobenzyl carbamate group, both as a conduit for the reductive activation of amine prodrugs, and as a possible novel protecting group for amines. Preliminary results describing some of this work have been reported previously.<sup>21</sup>

## Results and discussion

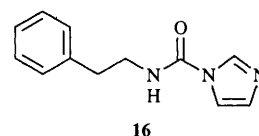
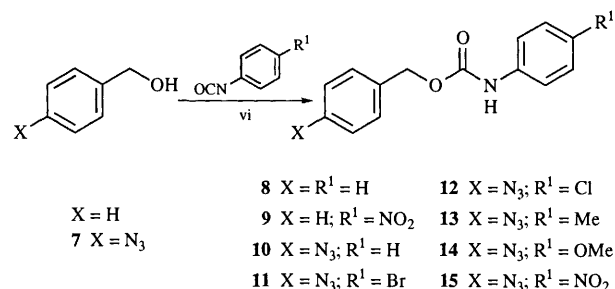
### Chemistry

4-Azidobenzyl alcohol **7** was readily prepared by the diazotisation-azidation of commercially available 4-aminobenzyl alcohol **6**, in 5 mol l<sup>-1</sup> aqueous hydrochloric acid (Scheme 2). Although moderately photosensitive, the azide proved sufficiently stable to allow recrystallisation from boiling ethyl acetate-light petroleum, and samples stored in the dark at 4 °C showed no evidence of decomposition after 12 months. In considering the most appropriate method for the preparation of ACBZ derivatives of amines, we were mindful of the importance of developing a synthetic route with general application, and one which would consistently afford high yields of the required carbamates. Benzyl *N*-arylcaramates **8–15** were conveniently prepared *via* a literature method<sup>22</sup> in good yields, by the base-catalysed reaction of benzyl or 4-azidobenzyl alcohol **7** with the appropriate aryl isocyanate. The presence of a trace contaminant, characterised (<sup>1</sup>H NMR, mass spectrum, and HPLC) as the corresponding bis(aryl)urea, and attributed to isocyanate hydrolysis by adventitious water, was invariably observed in these reactions. Fortuitously, bis(4-nitrophenyl)urea served as a useful internal standard for the kinetic studies (see below).

The obvious limitations of an isocyanate-based method for the preparation of ACBZ derivatives of amines (*e.g.* toxicity, side reactions) led us to investigate alternative approaches. Azolides, prepared by the reaction of amines with 1,1'-carbonyldiimidazole (CDI), are reportedly useful reagents for the synthesis of carbamates.<sup>23</sup> Thus, treatment of the model amine drug 2-phenylethylamine with CDI gave the azolide **16**, and subsequent reaction with the lithium alkoxide of **7** afforded the required azidobenzyl carbamate **17** in good yield. The stability of the azidobenzyl function to the vigorous reaction conditions employed was encouraging, but while perhaps applicable as a synthetic route to amine prodrugs, this approach is clearly inappropriate as a general method for the introduction of the ACBZ protecting group. Azidobenzyl chloroformate **18**, prepared in good yield by reacting 4-azidobenzyl alcohol with triphosgene in the presence of triethylamine, gave a meagre



- 20** R<sup>1</sup> = R<sup>2</sup> = CH<sub>2</sub>CH<sub>3</sub>      **23** R<sup>1</sup> = H R<sup>2</sup> = CH<sub>2</sub>CO<sub>2</sub>Me  
**21** R<sup>1</sup> = R<sup>2</sup> = CH<sub>2</sub>CH<sub>2</sub>OH      **24** R<sup>1</sup> = H R<sup>2</sup> = (CH<sub>2</sub>)<sub>4</sub>NH<sub>2</sub>  
**22** R<sup>1</sup> = H R<sup>2</sup> = CH<sub>2</sub>Ph      **25** R<sup>1</sup> = H R<sup>2</sup> = CH<sub>2</sub>CO<sub>2</sub>H



**Scheme 2** Reagents and conditions: i, NaNO<sub>2</sub> aq. HCl, 5 °C; NaN<sub>3</sub>; ii, O<sub>2</sub>N-4-PhOCOCl, pyridine, THF, 25 °C; iii, appropriate amine, pyridine or EtNPr<sub>2</sub>, THF, 25 °C; iv, BuLi, THF, 0 °C; v, Ph(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>, NEt<sub>3</sub>, THF; vi, NEt<sub>3</sub>, THF, 25 °C; Z = PhCH<sub>2</sub>OCO

yield of a product identical (TLC, <sup>1</sup>H NMR) to 4-azidobenzyl-*N*-(2-phenylethyl)carbamate **17** on treatment with 2-phenylethylamine. Unfortunately, **18** was isolated as an unstable oil which proved impossible to purify further, and the unfavourable properties of the chloroformate led us to consider other approaches.

4-Nitrophenyl carbonate derivatives have been successfully utilised for the selective *N*-acylation of amines; thus, *tert*-butyl 4-nitrophenyl carbonate is reportedly an excellent reagent for the mild conversion of amines into their BOC derivatives,<sup>24</sup> while selective CBZ protection of amines in the presence of alcohols has been achieved with benzyl 4-nitrophenyl carbonate under very mild conditions.<sup>25</sup> These results led us to investigate

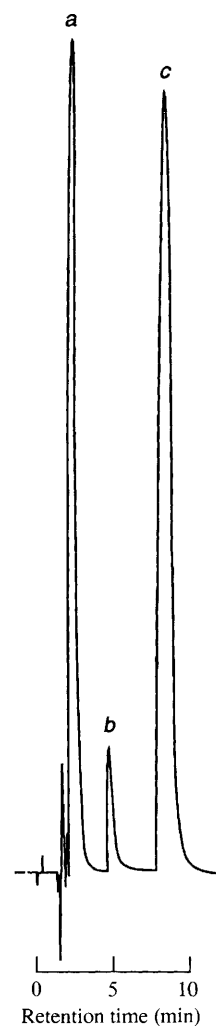
the possibility of using 4-azidobenzyl 4-nitrophenyl carbonate **19** for the conversion of amines into their ACBZ derivatives. This reagent was prepared in good yield by reacting **7** with 4-nitrophenyl chloroformate in the presence of pyridine<sup>26</sup> and, in contrast to the chloroformate **18**, the carbonate **19** was isolated as a stable crystalline solid (mp 101–102 °C), refrigerated samples of which have remained unchanged for over two years.

The conversion of representative amines into their ACBZ derivatives **20–24** proceeded smoothly, and in excellent yields, on treatment with carbonate **19** in the presence of pyridine or *N,N*-diisopropylethylamine. Removal of 4-nitrophenol was readily achieved by simply washing with 0.1 mol<sup>-1</sup> aqueous sodium hydroxide and, in most cases, the carbamates could be used without further purification. Selectivity for the amine function was confirmed on reaction of **19** with diethanolamine, which afforded the *N,N*-bis(2-hydroxyethyl)carbamate **21** exclusively, and, in keeping with previous studies with 4-nitrophenylcarbonates,<sup>25</sup> no evidence of competing *O*-acylation was observed. As expected, 4-azidobenzyl 4-nitrophenyl carbonate **19** also reacted readily with glycine methyl ester to give the corresponding ACBZ-glycine methyl ester **23** in high yield, and efficient conversion into the required ACBZ-glycine **25** occurred, without detriment to the azidobenzoyloxycarbonyl group, on treatment with potassium trimethylsilanoate<sup>27</sup> in THF.

Although aryl azides are readily converted into arylamines by a wide range of reductants, we sought a reducing system which would effect azide reduction selectively, and under mild reaction conditions, in the presence of other sensitive substituents. Knowles *et al.*<sup>8b,9</sup> reported that dithiols, including propane-1,3-dithiol and dithiothreitol (DTT), reduce azides rapidly under weakly basic conditions, and proposed a mechanism involving initial attack by thiolate anion on the azide, with subsequent cyclisation affording the corresponding amine and a cyclic disulfide, respectively. Treatment of 4-azidobenzyl *N*-4-nitrophenylcarbamate **15** with an excess of DTT, in the presence of triethylamine, gave the expected 4-nitroaniline in near quantitative yield, consistent with the reduction-fragmentation mechanism proposed in Scheme 1. Analogous reactions conducted with compounds **10**, **13** and **14** also furnished the appropriate anilines, and these reactions were subjected to a more detailed kinetic analysis, as described below. That this method of deprotection was not limited to arylamines, was established by treating the 4-azidobenzyl *N*-benzylcarbamate **22** with DTT, under identical conditions, to give the parent amine, benzylamine, in good yield. Thus, amines are readily converted to their ACBZ derivatives on treatment with 4-azidobenzyl 4-nitrophenyl carbonate, while DTT-mediated reduction represents an excellent method for the removal of this protecting group under relatively mild conditions. In a recent preliminary report, we have described an application of this approach in the synthesis of the polyamine derivative hirudonine.<sup>17</sup> Thus, ACBZ protection of the free *N*-4-position of 1,8-bis(trifluoroacetamido)spermidine, and subsequent deprotection of the terminal amino groups with methanolic ammonia, gave the *N*-4-ACBZ spermidine derivative in excellent yield. Nitroguanidation of the primary amines, followed by treatment with DTT-NEt<sub>3</sub> effected removal of the ACBZ group without concomitant reduction of the nitroguanidino functions, which were smoothly reduced to afford the target compound in excellent yield. The wider application of this novel orthogonal amine protecting group is currently under investigation.

#### Kinetic studies

Initial reductions of 4-azidobenzyl *N*-4-nitrophenylcarbamate **15** with dithiothreitol were attempted in aqueous tetrahydrofuran. It was found that complete reaction required the addition of base (10-fold excess) and an excess of dithiol (5-fold). Under these conditions, reduction was shown (TLC) to result in the



**Fig. 1** High-performance liquid chromatogram of the reduction of 4-azidobenzyl *N*-(4-nitrophenyl)carbamate **15** with dithiothreitol [*a*, 4-azidobenzyl alcohol; *b*, bis(4-nitrophenyl)urea; *c*, 4-azidobenzyl *N*-(4-nitrophenyl)carbamate]

liberation of 4-nitroaniline (as a bright yellow spot, *R<sub>f</sub>* 0.39) and 4-aminobenzyl alcohol (*R<sub>f</sub>* 0.14). Specificity for activation *via* the azido substituent was demonstrated, since a control reaction with benzyl *N*-4-nitrophenylcarbamate **9** failed to realise 4-nitroaniline under similar conditions, and left the starting material intact. The reduction also proceeded smoothly in alcoholic solvents but the solubility of the carbamates necessitated high levels of organic solvent (*e.g.* the solubility of 4-azidobenzyl carbamate **15** in methanol was *ca.* 1 mmol l<sup>-1</sup> and the addition of 5% water caused immediate precipitation). For most carbamates, this precluded the use of aqueous buffers (*e.g.* phosphates immediately precipitated) so final reduction conditions employed triethanolamine as the base and ethanol as the solvent. Here, reduction again proceeded smoothly with the expected products being identified by HPLC (4-nitroaniline, *t<sub>R</sub>* 1.6 min). The synthetic by-product, bis(4-nitrophenyl)urea served as a potential internal standard (*t<sub>R</sub>* 4.8 min) although its solubility was rather low (Fig. 1).

The reduction of aromatic azides has been shown to depend upon their electronic and steric environment<sup>28</sup> and, to assess the relative susceptibilities of the carbamates **10**, **13–15**, their reduction kinetics were followed. The use of a spectrophotometric assay to quantify 4-nitroaniline ( $\lambda_{\text{max}}$  350 nm) formation from **15** was compromised by interference from the cyclic disulfide ( $\lambda_{\text{max}}$  283 nm), arising from oxidation of DTT ( $\lambda_{\text{max}}$  230 nm), and the overlapping carbamate **15** ( $\lambda_{\text{max}}$  315 nm) absorption. Consequently, assays were undertaken by HPLC. Reactions were conducted under nitrogen, to minimise aerial

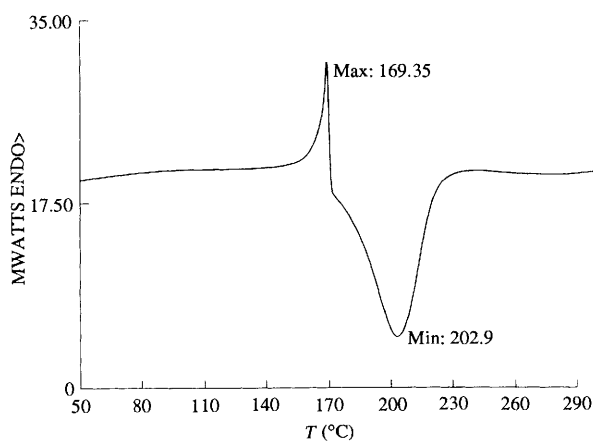


Fig. 2 Thermogram from differential scanning calorimetry of 4-azidobenzyl *N*-(4-nitrophenyl)carbamate showing melting endotherm ( $T_{\max}$  169.4 °C) followed by degradation exotherm ( $T_{\min}$  202.9 °C)

oxidation of the dithiothreitol, and in the dark to prevent photolysis of the azides.<sup>12,28</sup> Reactions followed a first-order model and, in this series, little difference was seen between the analogues. Indeed, the degradation rates of the parent 4-azidobenzyl *N*-phenylcarbamate **10** ( $k_1 \pm$  standard deviation,  $0.0581 \pm 0.013 \text{ h}^{-1}$ ), the 4-methyl- **13** ( $k_1$   $0.0640 \pm 0.011 \text{ h}^{-1}$ ) and the 4-methoxy- **14** ( $k_1$   $0.0587 \pm 0.013 \text{ h}^{-1}$ ) carbamates were almost indistinguishable. The reduction rate of 4-azidobenzyl *N*-4-nitrophenylcarbamate **15** was somewhat greater ( $k_1$   $0.114 \pm 0.011 \text{ h}^{-1}$ ) perhaps indicating a small dependence upon strong electron-withdrawal. The rate of disappearance of the parent carbamate and the rate of appearance of the arylamine were identical with no evidence for the presence of intermediates; an observation in accord with the cascade mechanism of the reaction shown in Scheme 1. The small differences between the degradation rates of the various 4-azidobenzyl-carbamates suggests that the rate-determining step is essentially reduction at  $\text{N}_3$  with cascade initiated by an increase in electron-donation ( $\text{N}_3$ ,  $\sigma_p = 0.15$ ;  $\text{NH}_2$ ,  $\sigma_p = -0.66$ ). The faster reaction of the nitro analogue **15** may indicate some electronic interaction [e.g. **15**  $\delta_{\text{H}}(\text{CH}_2) = 5.30$ ,  $k_1 = 0.114 \text{ h}^{-1}$ ; **14**,  $\delta_{\text{H}}(\text{CH}_2) = 5.22$ ,  $k_1 = 0.0587 \text{ h}^{-1}$ ] but dependence upon the substituent is weak.

With a higher concentration of DTT (increased from 12.5 to 125  $\text{mmol l}^{-1}$ ), little difference was observed between the azides **10**, **13** and **14**, which underwent reduction with an increased mean first-order rate constant of  $0.211 \pm 0.035 \text{ h}^{-1}$  while that for the nitro analogue **15** was, again, approximately double this value ( $0.479 \pm 0.084 \text{ h}^{-1}$ ). In a pseudo first-order reaction, the observed rate constant ( $k_1$ ) is related to the true second-order rate constant ( $k_2$ ) by:  $k_1 = [\text{B}_0] \cdot k_2$ , where  $[\text{B}_0]$  is the concentration of the reagent in excess, in this case, DTT. It is perhaps surprising, therefore, that a ten-fold increase in the concentration of DTT resulted in only an approximate quadrupling of the rate constant. This is a direct result of the importance of the disulfide anion,  $\text{p}K_{\text{a}}$  values 8.3 and 9.5,<sup>29</sup> in the rate-determining step.<sup>12,30</sup>

To assess the thermal properties of the carbamates, 4-azidobenzyl *N*-4-nitrophenylcarbamate **15** was subjected to differential scanning calorimetry (DSC). The thermogram was characterised by a sharp endothermic transition ( $T_{\text{onset}}$  163.5 °C). This reached a maximum ( $T_{\max}$  169.4 °C) before rapidly dropping to develop into a broad exothermic transition ( $T_{\text{onset}}$  179.4 °C,  $T_{\min}$  202.9 °C) (see Fig. 2). This pattern corresponds to that expected when degradation immediately follows melting; in this case, the thermally initiated loss of nitrogen.<sup>1</sup> This possibility was assessed by examining the contents of the DSC pan. A copious amount of a yellow sublimate was found and identified by spectroscopic analysis as 4-nitroaniline. Although this product probably arises *via* a

cascade reaction similar to that observed following azide reduction, fragmentation is presumably initiated by the thermal generation of an arylnitrene intermediate rather than an arylamine.

## Experimental

Ethanol refers to 95% ethanol; light petroleum refers to the fraction with bp 60–80 °C. Dry tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. All mps were recorded on an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Unicam SP200 Infrared spectrometer or a Nicolet 205X spectrophotometer. Mass spectra were recorded on a V.G. Micromass 12 instrument at 70 eV; source temperature 250–300 °C. UV spectra were recorded on a Pye Unicam SP8000 recording spectrophotometer. <sup>1</sup>H NMR spectra were recorded either on a Bruker Spectrospin AC 200E (200 MHz) or a Bruker WH 400 (400 MHz) spectrometer using tetramethylsilane as internal standard. Unless indicated otherwise, spectra were recorded in [<sup>2</sup>H<sub>6</sub>]DMSO as solvent. NH signals appeared as broad singlets exchangeable with D<sub>2</sub>O. Key: t = triplet, s = singlet, q = quartet, d = doublet, dd = double doublet, m = multiplet. The TLC systems employed aluminium sheets pre-coated with Kieselgel 60F<sub>254</sub> (0.2 mm) as the adsorbent, and either dichloromethane–methanol (9:1) or light petroleum–ethyl acetate (5:1) as the developing solvent. Column chromatography was conducted on silica gel (flash, Kieselgel 60). Elemental analyses were performed by Butterworth Laboratories, Middlesex.

### Differential scanning calorimetry

Differential scanning calorimetry was undertaken with a Perkin-Elmer DSC-4 instrument using the Thermal Analysis Data Station (TADS) for data collection, handling and presentation. Samples for thermal analysis were accurately weighed (1–4 mg) into an aluminium pan and covered with an aluminium lid which was then crimped into position. The pan was placed in the DSC oven together with a blank, prepared in exactly the same way but without the sample. The sample and blank were continuously purged with nitrogen gas at a flow-rate of 25  $\text{cm}^3 \text{ min}^{-1}$  (1.4  $\text{kg cm}^{-2}$ ) and the thermograms were recorded over a temperature range of 40–290 °C with a programmed heating rate of 10 °C  $\text{min}^{-1}$ . Temperature calibration was made with an indium standard (onset temperature 156.6 °C) and temperatures are quoted as those of transition onset ( $T_{\text{onset}}$ ) or of peak maximum ( $T_{\max}$ ) or minimum ( $T_{\min}$ ). Sublimates were extracted into chloroform and were identified spectroscopically.

### High-performance liquid chromatography

HPLC analyses were performed using a system constructed from an Altex 100A dual reciprocating, solvent-metering pump which delivered mobile phases at a flow rate of 1  $\text{ml min}^{-1}$  to a stainless steel column (10  $\text{cm} \times 4.6 \text{ mm}$ ) packed with 5  $\mu\text{m}$  Hypersil ODS (Shandon, UK) reversed-phase material. Samples were introduced through a Rheodyne 7120 injection valve fitted with a 100  $\mu\text{l}$  loop and UV detection was accomplished at 255 nm and 0.08–0.64 AUFS with a Pye Unicam LC3 variable wavelength UV detector equipped with a 8  $\mu\text{l}$  flow cell. Chromatograms were recorded using a JJ instruments CR452 chart recorder operated at a chart speed of 2  $\text{mm min}^{-1}$ . The mobile phase comprised aqueous acetonitrile (50%) containing 0.1% diethylamine with the pH adjusted to 2.5 with orthophosphoric acid. The retention times under these conditions were: 4-nitroaniline, 1.6 min; bis(4-nitrophenyl)urea 4.8 min; 4-azidobenzyl *N*-phenylcarbamate **10**, 5.8 min; 4-azidobenzyl *N*-4-bromophenyl-carbamate **11**, 11 min; 4-azidobenzyl *N*-4-chlorophenylcarbamate **12**, 11.8 min; 4-azidobenzyl *N*-4-methylphenylcarbamate **13**, 10.8 min; 4-azidobenzyl *N*-4-

methoxyphenylcarbamate **14**, 7.5 min; 4-azidobenzyl *N*-4-nitrophenylcarbamate **15**, 9 min. Final concentrations injected onto the column were: azide, 0.125 mmol l<sup>-1</sup> and butyl 4-hydroxybenzoate (4 min) as internal standard, 2 mmol l<sup>-1</sup>.

#### Thin-layer chromatography

TLC was effected on Kieselgel 60F<sub>254</sub> plastic sheets (0.2 mm) using a mobile phase comprising methanol (5% v/v) in chloroform. Chromatograms were visualised by irradiation at 254 nm to show components at *R<sub>f</sub>* values of 4-aminobenzyl alcohol (0.14); 4-azidobenzyl alcohol **7** (0.36); benzyl alcohol (0.37); 4-nitroaniline, as a bright yellow spot (0.39); benzyl *N*-4-nitrophenylcarbamate **9** (0.64); 4-azidobenzyl *N*-4-nitrophenylcarbamate **15** (0.66).

#### Reduction of azides with dithiothreitol

Aliquots (4 cm<sup>3</sup>) of solutions of each azide **10**, **13**, **14**, **15**, prepared in degassed ethanol (1 mmol l<sup>-1</sup>), were incubated at 37 °C and reduction was initiated by successive addition of triethanolamine (4 cm<sup>3</sup>, 100 mmol l<sup>-1</sup>) and dithiothreitol (8 cm<sup>3</sup>, 25 mmol l<sup>-1</sup>), each in ethanol at 37 °C, to give final concentrations of 0.25, 25 and 12.5 mmol l<sup>-1</sup> for azide, amine and DTT, respectively. Reaction mixtures were incubated at 37 °C, with the exclusion of light (to protect the photosensitive azides) and air (to prevent loss of DTT to the cyclic disulfide due to aerial oxidation) and, at appropriate intervals (0–10 h), samples (0.5 cm<sup>3</sup>) were withdrawn and quenched by addition to cold internal standard solution (0.5 cm<sup>3</sup>) prepared by mixing equal volumes of aqueous hydrochloric acid (0.1 mol l<sup>-1</sup>) and butyl 4-hydroxybenzoate (4 mmol l<sup>-1</sup>). The quenched solutions (100 μl) were analysed for residual azide by HPLC.

#### 4-Azidobenzyl alcohol **7**

To a stirred solution of 4-aminobenzyl alcohol **6** (2.0 g, 16 mmol) in 5 mol l<sup>-1</sup> hydrochloric acid (30 ml) at 0 °C, was added a solution of sodium nitrite (1.24 g, 18 mmol) in water (10 ml) over 30 min. Sodium azide (4.25 g, 65 mmol) was added in portions over 30 min, with vigorous effervescence, and the solution was stirred for a further 1 h at 0–5 °C. The reaction mixture was poured into ice-water, basified to pH 8 by the cautious addition of sodium bicarbonate, and extracted with ethyl acetate (2 × 50 ml). After washing with water and drying (MgSO<sub>4</sub>), the solvent was removed *in vacuo* to afford a yellow oil. Trituration with light petroleum and cooling at 4 °C for 24 h effected crystallisation, and, recrystallisation from ethyl acetate–light petroleum gave the required azide **7** as photosensitive cream needles (1.97 g, 81%), mp ~ 31–33 °C (decomp.) (Found: C, 56.62; H, 4.69; N, 27.74. C<sub>7</sub>H<sub>7</sub>N<sub>3</sub>O requires C, 56.37; H, 4.73; N, 28.17%); *v*<sub>max</sub>(Nujol)/cm<sup>-1</sup> 3300, 2100 and 1290; *δ*<sub>H</sub>(CDCl<sub>3</sub>) 4.60 (2 H, d, *J* 6, PhCH<sub>2</sub>), 5.36 (1 H, m, *J* 6, OH), 7.19 (2 H, d, *J* 8, C-2 and C-6), 7.48 (2 H, d, *J* 8, C-3 and C-5); *m/z* 149 (M<sup>+</sup>), 121, 91, 76, 66.

#### *N*-(2-Phenethyl)-*N'*-imidazoylurea **16**

2-Phenylethylamine (0.4 g, 3.3 mmol) in THF (5 ml) was added dropwise to a stirred solution of 1,1'-carbonyldiimidazole (0.6 g, 3.6 mmol) in THF (10 ml) over 15 min. The mixture was stirred for a further 30 min at 25 °C and the solvent was removed under reduced pressure. The solid residue was redissolved in ethyl acetate (50 ml), washed with water (25 ml) and dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo* to afford the azolide **16** (0.73 g, 68.5%). Recrystallisation from ethyl acetate gave the analytical sample as white microprisms, mp 104–105 °C (Found: C, 64.79; H, 5.62; N, 18.75. C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O·0.4H<sub>2</sub>O requires C, 64.73; H, 6.20; N, 18.88%); *v*<sub>max</sub>(KBr disc)/cm<sup>-1</sup> 3199, 3026, 1707 and 1548; *δ*<sub>H</sub> 2.97 (2 H, t, *J* 7, PhCH<sub>2</sub>CH<sub>2</sub>), 3.59 (2 H, m, PhCH<sub>2</sub>CH<sub>2</sub>), 7.13 (1 H, d, imidazole C-4), 7.37 (5 H, m, Ph), 7.75 (1 H, d, imidazole C-5), 8.32 (1 H, s, imidazole C-2), 8.72 (1 H, t, NH); *m/z* 147 (M<sup>+</sup> - 1 - C<sub>3</sub>H<sub>3</sub>N<sub>2</sub>, 78%), 104 (20), 91 (100).

#### 4-Azidobenzyl *N*-(2-phenylethyl)carbamate **17**

To a solution of 4-azidobenzyl alcohol **7** (0.38 g, 2.5 mmol) in THF (10 ml), under argon, was added a solution of butyllithium in pentanol (2 mol l<sup>-1</sup>, 1.45 ml), and the mixture was stirred for 15 min. A solution of *N*-(2-phenethyl)-*N'*-imidazoylurea (0.50 g, 2.2 mmol) in THF (10 ml) was added dropwise over 20 min, and the reaction mixture was stirred for 24 h at 25 °C. After filtration, the solvents were evaporated to afford a yellow solid. Chromatography on silica gel, employing light petroleum–ethyl acetate (3:1) as eluent, afforded the *phenethyl carbamate 17* as pale yellow flakes (0.28 g, 43%), mp 95–96 °C (Found: C, 65.13; H, 5.34; N, 18.81. C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub> requires C, 64.85; H, 5.44; N, 18.91%); *v*<sub>max</sub>(KBr disc)/cm<sup>-1</sup> 3315, 2117, 2094, 1682, 1540 and 1508; *δ*<sub>H</sub> 2.82 (2 H, t, PhCH<sub>2</sub>CH<sub>2</sub>NH) 3.34 (2 H, m, PhCH<sub>2</sub>CH<sub>2</sub>NH) 5.10 (2 H, s, CH<sub>2</sub>), 7.24 (2 H, d, *J* 8.4, Ph-4-N<sub>3</sub> C-2 and C-6), 7.28–7.40 (6 H, m, Ph + NH), 7.48 (2 H, d, *J* 8.4, Ph-4-N<sub>3</sub> C-3 and C-5); *m/z* 296 (M<sup>+</sup>, 20%), 286 (39), 105 (100), 91 (65).

#### 4-Azidobenzyl chloroformate **18**

To a stirred solution of triphosgene (1.0 g, 3.4 mmol) and 4-azidobenzyl alcohol **7** (1.0 g, 6.7 mmol) in THF (40 ml), was added triethylamine (2.0 g, 19.7 mmol) in THF (40 ml) dropwise over 1 h. The mixture was stirred under nitrogen in the dark for 72 h at 25 °C and, after removal of solvent, the residue was partially redissolved in ethyl acetate (25 ml) and filtered through Kieselguhr. The filtrate was washed with water (2 × 25 ml), dried (MgSO<sub>4</sub>), and the solvent was evaporated under reduced pressure to give the chloroformate **18** as a photosensitive viscous yellow oil (0.83 g, 58%) which was used without further purification; *v*<sub>max</sub>(Nujol)/cm<sup>-1</sup> 2110, 1736 and 1260; *δ*<sub>H</sub>(CDCl<sub>3</sub>) 4.50 (2 H, s, CH<sub>2</sub>), 6.95 (2 H, d, *J* 8.5, C-2 and C-6), 7.30 (2 H, d, *J* 8.5, C-3 and C-5). Treatment of a stirred solution of **18** (0.83 g, 3.9 mmol) in THF (20 ml), containing triethylamine (0.4 g, 4.8 mmol), with 2-phenylethylamine (0.54 g, 4.4 mmol) afforded, after 12 h, a product (0.1 g) identical (TLC, <sup>1</sup>H NMR) to 4-azidobenzyl *N*-(2-phenylethyl) carbamate **17** prepared as described above.

#### 4-Azidobenzyl 4-nitrophenyl carbonate **19**

A solution of 4-nitrophenyl chloroformate (4.1 g, 20 mmol) and pyridine (3.5 g, 42 mmol) in THF (70 ml) was stirred at 0 °C, and 4-azidobenzyl alcohol **7** (3.0 g, 20 mmol) in THF (100 ml) was added over 30 min. The mixture was stirred in the dark for 72 h at 25 °C, when all starting materials were consumed (TLC), and the solvent was evaporated under reduced pressure. The residual solid was redissolved in ethyl acetate (50 ml), washed with water (2 × 50 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was evaporated and the residual yellow powder recrystallised twice from ethyl acetate–light petroleum to furnish the carbonate **19** as pale yellow needles (4.1 g, 65%), mp 101–102 °C (Found: C, 53.61; H, 3.28; N, 17.87. C<sub>14</sub>H<sub>10</sub>N<sub>3</sub>O<sub>5</sub> requires C, 53.51; H, 3.21; N, 17.83%); *v*<sub>max</sub>(Nujol)/cm<sup>-1</sup> 3114, 3083, 2120, 1755, 1520, 1503 and 1351; *δ*<sub>H</sub> 5.40 (2 H, s, CH<sub>2</sub>), 7.27 (2 H, d, *J* 8.4, Ar), 7.61–7.70 (4 H, m, Ar), 8.44 (2 H, d, *J* 9.1, Ar); *δ*<sub>C</sub> 70.16, 119.60, 122.90, 125.73, 130.81, 131.83, 140.18, 145.51, 152.27 and 155.61; *m/z* 314 (M<sup>+</sup>, 33%), 286 (22), 120 (55), 104 (100).

#### 4-Azidobenzyl carbamates

**General method A.** In a typical reaction a solution of 4-nitrophenyl isocyanate (0.99 g, 6 mmol), in dry THF (10 ml), was added dropwise over 15 min to a stirred solution of 4-azidobenzyl alcohol **7** (0.9 g, 6 mmol) and triethylamine (0.2 g) in dry THF (20 ml). The reaction mixture was stirred at 25 °C for 24 h, with protection from light. Solvents were evaporated under reduced pressure to afford a yellow solid, and recrystallisation from ethyl acetate–light petroleum afforded 4-azidobenzyl *N*-(4-nitrophenyl)carbamate **15** as yellow microcrystals (1.64 g, 87%), mp 169–170 °C (Found: C, 53.33; H, 3.51; N, 22.13. C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>O<sub>4</sub> requires C, 53.67; H, 3.54; N, 22.36%);

$\nu_{\max}$ (KBr disc)/ $\text{cm}^{-1}$  3389, 2130, 1742, 1542 and 1331;  $\delta_{\text{H}}$  5.30 (2 H, s,  $\text{PhCH}_2$ ), 7.28 (2 H, d,  $J$  8.4, Ph-4- $\text{N}_3$  C-2 and C-6), 7.62 (2 H, d,  $J$  7.8, Ph-4- $\text{N}_3$  C-3 and C-5), 7.82 (2 H, d,  $J$  9.2, Ph-4- $\text{NO}_2$  C-2 and C-6), 8.33 (2 H, d,  $J$  9.2, Ph-4- $\text{NO}_2$  C-3 and C-5), 10.62 (1 H, br s, NH);  $m/z$  313 ( $\text{M}^+$ ), 285, 165, 148, 138, 121, 104.

Similar reactions carried out with **7** and the appropriate isocyanate gave the required azidobenzylcarbamates **8** to **14**, which were purified by recrystallisation from ethyl acetate–light petroleum.

**Benzyl *N*-phenylcarbamate 8.** Prepared from phenyl isocyanate (1.0 g, 8.4 mmol) and benzyl alcohol (0.91 g, 8.4 mmol) in 63% yield. White needles, mp 76 °C (lit.,<sup>31</sup> mp 77 °C) (Found: C, 74.04; H, 5.77; N, 6.11.  $\text{C}_{14}\text{H}_{13}\text{NO}_2$  requires C, 73.99; H, 5.77; N, 6.16%);  $\nu_{\max}$ (Nujol)/ $\text{cm}^{-1}$  3273, 1690 and 1548;  $\delta_{\text{H}}$  5.27 (2 H, s,  $\text{CH}_2$ ), 7.10 (1 H, t, Ar), 7.35–7.61 (9 H, m, 2  $\times$  Ar), 9.50 (1 H, NH);  $m/z$  227 ( $\text{M}^+$ ), 183, 120, 91.

**Benzyl *N*-(4-nitrophenyl)carbamate 9.** Prepared from 4-nitrophenyl isocyanate (1.0 g, 6.1 mmol) and benzyl alcohol (0.73 g, 6.7 mmol) in 83% yield. Yellow microprisms, mp 152–153 °C (lit.,<sup>22</sup> mp 155 °C) (Found: C, 62.01; H, 4.60; N, 10.39.  $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_4$  requires C, 61.76; H, 4.44; N, 10.29%);  $\nu_{\max}$ (Nujol)/ $\text{cm}^{-1}$  3338, 1742, 1547 and 1347;  $\delta_{\text{H}}$  5.32 (2 H, s,  $\text{PhCH}_2$ ), 7.43–7.55 (5 H, m,  $\text{PhCH}_2\text{O}$ ), 7.82 (2 H, d,  $J$  9.1, Ph-4- $\text{NO}_2$  C-2 and C-6), 8.33 (2 H, d,  $J$  9.1, Ph-4- $\text{NO}_2$  C-3 and C-5), 10.63 (1 H, br s, NH);  $m/z$  272 ( $\text{M}^+$ ), 285, 164, 134, 118, 117, 91.

**4-Azidobenzyl *N*-phenylcarbamate 10.** Prepared from phenyl isocyanate (0.66 g, 5.5 mmol) and 4-azidobenzyl alcohol (0.75 g, 5.0 mmol) in 53% yield. Buff needles, mp 107–108 °C (Found: C, 62.44; H, 4.60; N, 21.20.  $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_2$  requires C, 62.68; H, 4.51; N, 20.88%);  $\nu_{\max}$ (Nujol)/ $\text{cm}^{-1}$  3300, 2100 and 1700;  $\delta_{\text{H}}$  5.24 (2 H, s,  $\text{PhCH}_2$ ), 7.10 (1 H, m, Ph-C-4), 7.26 (2 H, d,  $J$  8.3, Ph-4- $\text{N}_3$  C-2 and C-6), 7.39 (2 H, m, Ph-C-3 and Ph-C-5), 7.58 (2 H, d, Ph-C-2 and Ph-C-6), 7.59 (2 H, d,  $J$  8.3, Ph-4- $\text{N}_3$  C-3 and C-5), 9.3 (1 H, br s, NH);  $m/z$  268 ( $\text{M}^+$ ), 240, 149, 132, 104, 92.

**4-Azidobenzyl *N*-(4-bromophenyl)carbamate 11.** Prepared from 4-bromophenyl isocyanate (2.66 g, 13 mmol) and 4-azidobenzyl alcohol (2.0 g, 13 mmol) in 80% yield. Off-white needles, mp 140 °C (Found: C, 48.21; H, 3.15; N, 16.10.  $\text{C}_{14}\text{H}_{11}\text{N}_4\text{O}_2\text{Br}$  requires C, 48.44; H, 3.19; N, 16.14%);  $\nu_{\max}$ (KBr disc)/ $\text{cm}^{-1}$  3338, 2122, 2089, 1702 and 1530;  $\delta_{\text{H}}$  5.24 (2 H, s,  $\text{PhCH}_2$ ), 7.26 (2 H, d,  $J$  8.3, Ph-4- $\text{N}_3$  C-2 and C-6), 7.56 (4 H, br s, Ph-4-Br), 7.58 (2 H, d,  $J$  8.3, Ph-4- $\text{N}_3$  C-3 and C-5), 10.20 (1 H, br s, NH);  $m/z$  346 [348] ( $\text{M}^+$ ), 318 [320], 302 [304], 197 [199], 132, 104.

**4-Azidobenzyl *N*-(4-chlorophenyl)carbamate 12.** Prepared from 4-chlorophenyl isocyanate (0.92 g, 6.0 mmol) and 4-azidobenzyl alcohol (0.9 g, 6.0 mmol) in 24.2% yield. Buff needles, mp 133–134 °C (Found: C, 55.24; H, 3.63; N, 18.48.  $\text{C}_{14}\text{H}_{11}\text{N}_4\text{O}_2\text{Cl}$  requires C, 55.55; H, 3.66; N, 18.51%);  $\nu_{\max}$ (Nujol)/ $\text{cm}^{-1}$  3321, 2121, 1699 and 1529;  $\delta_{\text{H}}$  5.24 (2 H, s,  $\text{PhCH}_2$ ), 7.26 (2 H, d,  $J$  8.4, Ph-4- $\text{N}_3$  C-2 and C-6), 7.45 (2 H, d,  $J$  8.9, Ph-4-Cl C-2 and C-6), 7.58–7.62 (4 H, m, 2  $\times$  Ar) 10.1 (1 H, br s, NH);  $m/z$  302 [304] ( $\text{M}^+$ ), 274 [276], 230 [232], 132, 104.

**4-Azidobenzyl *N*-(4-methylphenyl)carbamate 13.** Prepared from *p*-tolyl isocyanate (2.0 g, 13 mmol) and 4-azidobenzyl alcohol (1.79 g, 13 mmol) in 74% yield. Pale yellow needles, mp 117–118 °C (Found: C, 63.50; H, 4.80; N, 20.0.  $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_2$  requires C, 63.82; H, 5.0; N, 19.85%);  $\nu_{\max}$ (KBr disc)/ $\text{cm}^{-1}$  3293, 2125, 1695, 1527 and 1508;  $\delta_{\text{H}}$  2.34 (3 H, s,  $\text{PhCH}_3$ ), 5.23 (2 H, s,  $\text{PhCH}_2$ ), 7.19 (2 H, d,  $J$  8.3, Ph-4- $\text{N}_3$  C-2 and C-6), 7.26 (2 H, d,  $J$  8.2, Ph-4-Me C-3 and C-5), 7.46 (2 H, d,  $J$  8.2, Ph-4-Me C-2 and C-6), 7.58 (2 H, d,  $J$  8.3, Ph-4- $\text{N}_3$  C-3 and C-5), 8.8 (1 H, br s, NH);  $m/z$  282 ( $\text{M}^+$ ), 238, 184, 149, 132, 104.

**4-Azidobenzyl *N*-(4-methoxyphenyl)carbamate 14.** Prepared from 4-methoxyphenyl isocyanate (1.0 g, 6.7 mmol) and 4-azidobenzyl alcohol (1.0 g, 6.7 mmol) in 30% yield. Yellow flakes, mp 107–108 °C (Found: C, 60.10; H, 4.74; N, 18.68.

$\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_3$  requires C, 60.40; H, 4.73; N, 18.78%);  $\nu_{\max}$ (KBr disc)/ $\text{cm}^{-1}$  3323, 2118, 1701, 1527 and 1508;  $\delta_{\text{H}}$  3.82 (3 H, s,  $\text{PhOCH}_3$ ), 5.22 (2 H, s,  $\text{PhCH}_2$ ), 6.98 (2 H, d,  $J$  8.5, Ph-4-OMe C-3 and C-5), 7.26 (2 H, d,  $J$  8.3, Ph-4- $\text{N}_3$  C-2 and C-6), 7.48 (2 H, d,  $J$  8.5, Ph-4-OMe C-2 and C-6), 7.58 (2 H, d,  $J$  8.3, Ph-4- $\text{N}_3$  C-3 and C-5), 7.00 (1 H, br s, NH);  $m/z$  272 ( $\text{M}^+$ ), 285, 164, 134, 118, 117, 91.

#### General method B

Typically, a solution of 4-azidobenzyl 4-nitrophenyl carbonate **19** (0.3 g, 1 mmol) in THF (5 ml) was stirred at 0 °C, with protection from light, and benzylamine (0.16 g, 1.5 mmol) and pyridine (0.2 g, 0.24 mmol) were added. The solution was stirred for 12 h at 25 °C, solvents were evaporated, and the residual yellow solid was redissolved in dichloromethane (30 ml). After sequential washing with water (2  $\times$  30 ml), aqueous sodium hydroxide (0.1 mol  $\text{l}^{-1}$ , 2  $\times$  30 ml), and water (2  $\times$  30 ml), the organic layer was dried ( $\text{MgSO}_4$ ) and the solvent removed *in vacuo*. Purification by chromatography on silica gel, with dichloromethane as eluent, furnished 4-azidobenzyl *N*-benzylcarbamate **22** (0.23 g, 84%) as cream microprisms, mp 83–84 °C (Found: C, 63.92; H, 5.05; N, 19.75.  $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_2$  requires C, 63.82; H, 5.00; N, 19.85%);  $\nu_{\max}$ (KBr)/ $\text{cm}^{-1}$  3433, 2118 and 1694;  $\delta_{\text{H}}$  4.30 (2 H, d,  $J$  6.1,  $\text{ArCH}_2\text{NH}$ ), 5.13 (2 H, s,  $\text{ArCH}_2\text{O}$ ), 7.23 (2 H, d,  $J$  8.5, C-2 and C-6), 7.38 (5 H, m, Ph), 7.51 (2 H, d,  $J$  8.5, C-3 and C-5), 7.95 (1 H, t,  $J$  6.1,  $\text{ArCH}_2\text{NH}$ );  $m/z$  282 ( $\text{M}^+$ ), 254, 104, 91.

Similar reactions carried out with **19** and the appropriate amine gave the required azidobenzylcarbamates **20**, **21**, **23** and **24**. For those reactions involving amine salts, *N*-ethyl-diisopropylamine replaced pyridine as base.

**4-Azidobenzyl *N,N*-diethylcarbamate 20.** Prepared from **19** (0.30 g, 1.0 mmol) and diethylamine (0.08 g, 1.1 mmol) in 91% yield. Colourless oil (Found: C, 57.59; H, 6.37; N, 22.24.  $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_2 \cdot 0.063 \text{H}_2\text{O}$  requires C, 57.75; H, 6.47; N, 22.46%);  $\nu_{\max}$ (film)/ $\text{cm}^{-1}$  3389, 2976, 2112 and 1703;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 1.05 (6 H, t, 2  $\times$   $\text{CH}_3$ ), 3.23 (4 H, q, 2  $\times$   $\text{CH}_2$ ), 5.02 (2 H, s,  $\text{CH}_2$ ), 6.94 (2 H, d,  $J$  8.5, C-2 and C-6), 7.29 (2 H, d,  $J$  8.5, C-3 and C-5);  $m/z$  248 ( $\text{M}^+$ ), 220, 100, 72.

**4-Azidobenzyl *N,N*-bis(2-hydroxyethyl)carbamate 21.** Prepared from **19** (0.5 g, 1.67 mmol) and diethanolamine (0.19 g, 1.84 mmol) in 85% yield. Colourless oil;  $\nu_{\max}$ (film)/ $\text{cm}^{-1}$  3394, 2117, 1683 and 1509;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 2.88 (2 H, br s, 2  $\times$  OH), 3.48 (4 H, m, 2  $\times$   $\text{CH}_2$ ), 3.79 (4 H, m, 2  $\times$   $\text{CH}_2$ ), 5.07 (2 H, s,  $\text{ArCH}_2$ ), 6.98 (2 H, d,  $J$  8.5, C-2 and C-6), 7.32 (2 H, d,  $J$  8.5, C-3 and C-5);  $m/z$  252 ( $\text{M}^+ - \text{N}_2$ ), 132, 104, 77.

**Methyl 4-azidobenzyl *N*-carboxymethylcarbamate 23.** Prepared from **19** (0.76 g, 2.39 mmol) and glycine methyl ester hydrochloride (0.30 g, 2.39 mmol) in 90% yield. Pale yellow microprisms, mp 65–66 °C [purified by chromatography on silica gel with light petroleum–ethyl acetate (4:1) as eluent] (Found: C, 50.18; H, 4.39; N, 20.94.  $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_4$  requires C, 50.00; H, 4.58; N, 21.20%);  $\nu_{\max}$ (KBr)/ $\text{cm}^{-1}$  3346, 2116, 1744 and 1688;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 3.74 (3 H, t,  $\text{CO}_2\text{CH}_3$ ), 3.97 (2 H, d,  $J$  5.6,  $\text{CH}_2\text{CO}_2\text{Me}$ ), 5.07 (2 H, s,  $\text{ArCH}_2$ ), 5.24 (1 H, br s, NH) 6.99 (2 H, d,  $J$  8.5, C-2 and C-6), 7.34 (2 H, d,  $J$  8.5, C-3 and C-5);  $\delta_{\text{C}}$  42.66, 52.40, 66.49, 119.14, 129.84, 133.02, 140.03, 156.40, and 171.60;  $m/z$  264 ( $\text{M}^+ 20\%$ ), 236 (28), 221 (3), 176 (48), 132 (35), 88 (62).

***N*<sup>1</sup>-4-Azidobenzylloxycarbonyl-*N*<sup>4</sup>-benzylloxycarbonyl-1,4-diaminobutane 24.** Prepared from **19** (0.30 g, 1.0 mmol) and *N*-benzylloxycarbonyl-1,4-diaminobutane hydrochloride (0.272 g, 1.1 mmol) in 100% yield. White powder, mp 95–96 °C (Found: C, 60.83; H, 5.99; N, 17.76.  $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_4$  requires C, 60.43; H, 5.84; N, 17.63%);  $\nu_{\max}$ (KBr)/ $\text{cm}^{-1}$  3325, 2118, 1684 and 1530;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 1.46 (4 H, br s, 2  $\times$   $\text{CH}_2$ ), 3.13 (4 H, m, 2  $\times$   $\text{CH}_2\text{NH}$ ), 4.74 (2 H, br s, NH), 4.98 (2 H, s,  $\text{ArCH}_2$ ), 5.02 (2 H, s,  $\text{ArCH}_2$ ), 6.94 (2 H, d,  $J$  8.5, C-2 and C-6), 7.28 (5 H, br s, Ph), 7.27 (2 H, d,  $J$  8.5, C-3 and C-5);  $m/z$  (FAB, *m*-nitrobenzyl alcohol) 398 ( $\text{M}^+ + 1$ ).

**4-Azidobenzyl N-carboxymethylcarbamate 25.** A solution of the carbamate ester **23** (0.27 g, 1.01 mmol) in THF (2 ml) was added dropwise, over 5 min, to a vigorously stirred suspension of potassium trimethylsilanoate (0.144 g, 1.12 mmol) in THF (10 ml). The mixture was stirred for 6 h at 25 °C, the solvent was evaporated under reduced pressure, and the residual yellow solid was redissolved in water (20 ml). After washing with ethyl acetate (2 × 10 ml), the aqueous layer was acidified to pH 2 with aqueous hydrochloric acid (0.1 mol l<sup>-1</sup>), and extracted with ethyl acetate (2 × 10 ml). The combined organic layers were washed with water (2 × 20 ml), dried (MgSO<sub>4</sub>), and evaporated *in vacuo* to give an off-white solid. Chromatography on silica gel, employing light petroleum–ethyl acetate (4:1) as eluent, furnished 4-azidobenzyl glycine carbamate **25** as cream flakes (0.22 g, 86.5%), mp 101–103 °C (Found: C, 48.35; H, 3.89; N, 21.92. C<sub>10</sub>H<sub>10</sub>N<sub>4</sub>O<sub>4</sub> requires C, 48.00; H, 4.03; N, 22.40%);  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3337, 3050, 2979, 2960, 2945, 2125, 1692, 1544 and 1509;  $\delta_{\text{H}}(\text{CDCl}_3)$  4.01 (2 H, d, NHCH<sub>2</sub>CO), 5.07 (2 H, s, ArCH<sub>2</sub>), 5.30 (1 H, br t, NH) 6.98 (2 H, d, *J* 8.5, C-2 and C-6), 7.33 (2 H, d, *J* 8.5, C-3 and C-5) 8.10 (1 H, br s, CO<sub>2</sub>H);  $\delta_{\text{C}}$  42.44, 65.24, 119.37, 129.96, 134.26, 139.26, 156.76 and 171.891; *m/z* 250 (M<sup>+</sup>), 222, 176, 104, 93.

#### Liberation of benzylamine from 4-azidobenzyl N-benzylcarbamate **22**

A mixture of the azidocarbamate **22** (0.1 g, 0.4 mmol), dithiothreitol (0.2 g, 1.3 mmol), and triethylamine (0.2 g, 2.0 mmol) in methanol (10 ml) was stirred at 25 °C under nitrogen for 12 h. Solvents were removed under reduced pressure and the residual solid was redissolved in hydrochloric acid (0.5 mol l<sup>-1</sup>, 10 ml), filtered, washed with dichloromethane (2 × 20 ml), and basified to pH 8.0 with aqueous sodium hydroxide (0.5 mol l<sup>-1</sup>). Subsequent extraction with dichloromethane (2 × 20 ml) afforded, after drying (MgSO<sub>4</sub>) and removal of solvent, a colourless liquid (0.0028 g, 65%) which proved identical (<sup>1</sup>H NMR and MS) to an authentic sample of benzylamine.

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