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LETTERS

# Photochemical alkylation of glycine leading to phenylalanines

Haydn S. Knowles,<sup>a</sup> Keith Hunt<sup>b</sup> and Andrew F. Parsons<sup>a,\*</sup><sup>a</sup>*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*<sup>b</sup>*A. H. Marks and Co. Ltd, Wyke, Bradford, West Yorkshire BD12 9EJ, UK*

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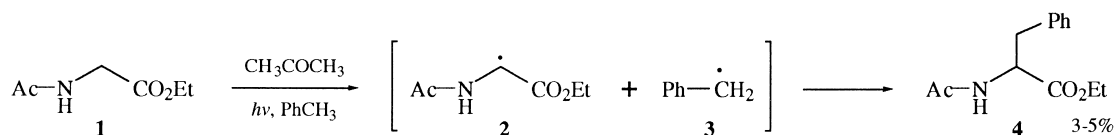
## Abstract

UV photolysis of protected glycines in the presence of di-*tert*-butyl peroxide, benzophenone and substituted toluenes is shown to lead to selective alkylation at the  $\alpha$ -position. Phenylalanines are isolated in yields of generally > 50% (based on recovered starting material). © 2000 Elsevier Science Ltd. All rights reserved.

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The considerable diversity and biological importance of  $\alpha$ -amino acids has attracted the attention of organic chemists for many years.<sup>1</sup> Of particular interest are phenylalanine derivatives because of the medicinal importance of compounds such as dopa, melphalan and levothyroxin, which are used in the treatment of Parkinson's disease, cancer and myxoedema, respectively. These types of compounds are generally prepared using ionic reactions.<sup>1</sup> In comparison, the preparation of  $\alpha$ -amino acids using radical carbon–carbon bond-forming reactions has received considerably less attention.<sup>2</sup> This is surprising bearing in mind the mild (neutral) reaction conditions employed and the compatibility of radicals with a wide range of common functional groups (including amides and esters).

The formation of glycine derivatives by an intermolecular radical coupling reaction was first reported by Elad and co-workers (Scheme 1).<sup>3</sup> They showed that UV irradiation of *N*-acetyl-glycine ethyl ester **1** in the presence of acetone and (excess) toluene led to the selective formation

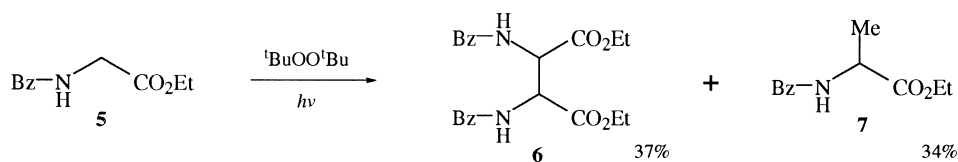


Scheme 1.

\* Corresponding author. Tel: +44-1904-432608; fax: +44-1904-432516; e-mail: afp2@york.ac.uk

of phenylalanine **4**, although the yield was only 3–5%. The proposed mechanism for this reaction involved coupling of captodative radical **2** with a benzyl radical **3**, these radicals being derived from abstraction of a hydrogen atom from **1** and toluene, respectively, by an excited acetone molecule. This method was extended to alkylation of glycine residues within peptides and proteins, and this could be accomplished using visible light, when an  $\alpha$ -diketone and di-*tert*-butyl peroxide were used in place of acetone.<sup>4</sup>

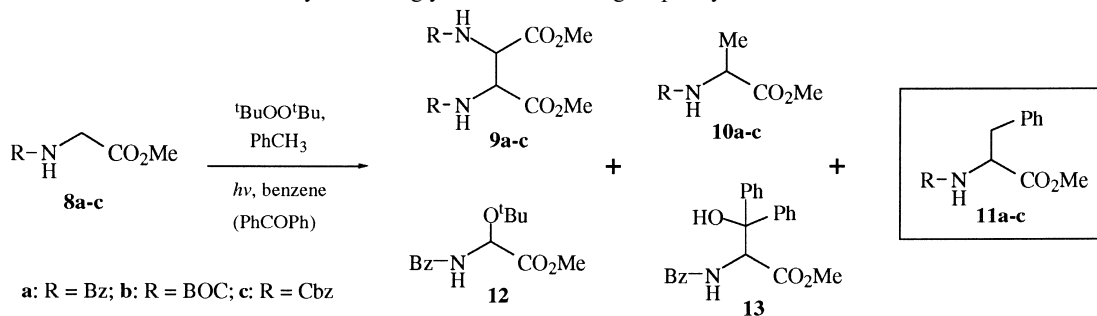
More recently, these radical coupling reactions have been carried out in the absence of an alkylating agent, to form amino acid dimers.<sup>5</sup> Easton and co-workers<sup>6</sup> have reported the formation of butanedioate **6** in 37% yield on UV irradiation of a mixture of glycine **5** and di-*tert*-butyl peroxide (Scheme 2). In this reaction it is *tert*-butoxyl radical, or methyl radical (produced on  $\beta$ -scission of  $^t\text{BuO}\cdot$ ), that abstracts the  $\alpha$ -hydrogen atom from **5**. Although the use of di-*tert*-butyl peroxide, in place of acetone, leads to more efficient hydrogen-atom abstraction, as methyl radicals are produced, a competitive coupling to form alanine **7** (in 34% yield) was also observed. With a view to developing an efficient photochemical approach to phenylalanines, this paper reports the alkylation of various glycine derivatives using di-*tert*-butyl peroxide (as the initiator) in the presence of substituted toluenes for the first time.



Scheme 2.

Initial investigations centred on UV irradiation of **8a** in the presence of toluene and di-*tert*-butyl peroxide (Table 1). The mixture was irradiated using a 125 W lamp in degassed benzene and a variety of reactions were carried out using different concentrations of the reagents. In all cases, 1,2-diphenylethane (derived from dimerisation of **3**) and small amounts of butanedioate **9a** and alanine **10a** were isolated, but the major product was the desired phenylalanine **11a**. The reaction was most selective for **11a** when a 1:2:5 ratio of **8a**:peroxide:toluene was used; under these conditions **11a** was formed in 27% yield, or 59% yield based on recovered **8a** (entry 1).<sup>7</sup> Similar results were obtained using *N*-Boc and *N*-Cbz protected glycines **8b** and **8c**, to form **11b** and **11c**, respectively (entries 2 and 3). The selective alkylation of **8c** is of particular note because (competitive) hydrogen-atom abstraction at the benzylic position of the Cbz-protecting group is also possible although no products derived from this reaction were isolated.<sup>8</sup> With a view to decreasing the reaction time, the alkylation of **8a** was also carried out using a 400 W UV lamp (entry 4) and although the total yield of products increased (from 70 to 91%), an additional product, namely  $\alpha$ -*tert*-butoxy-glycine **12**, was isolated in 13% yield. The formation of **12** presumably reflects a higher concentration of the  $^t\text{BuO}\cdot$  radical (which couples with the captodative radical) when using the more powerful lamp, but the yield of **12** could be minimised by increasing the concentration of **8a** (entry 5). Further experiments investigated the addition of photosensitisers and when benzophenone<sup>9</sup> was used in combination with 10 equivalents of toluene an optimum yield of 37% (or 57% based on recovered **8a**) was isolated for **11a** (entries 6 and 7). The use of benzophenone also produced minor amounts of the serine derivative **13**, derived from coupling of the captodative radical with  $\text{Ph}_2(\text{HO})\text{C}\cdot$ . Indeed, when the same photolysis was carried out in the absence of toluene, **13** was isolated in 23% yield (or 50% based on recovered **8a**).<sup>10</sup>

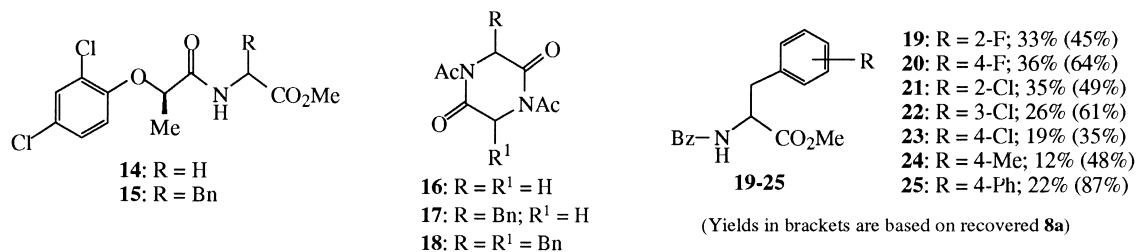
Table 1  
Photoalkylation of glycines **8a-c** leading to phenylalanines **11a-c**



Entry	<b>8</b>	Reaction Conditions	Conc <sup>a</sup> of <b>8</b> /mol dm <sup>-3</sup>	Equiv. of peroxide	Equiv. of toluene	<b>9a-c</b> (%) <sup>b</sup>	<b>10a-c</b> (%) <sup>b</sup>	<b>11a-c</b> (%) <sup>b</sup>	<b>12</b> (%) <sup>b</sup>	<b>13</b> (%) <sup>b</sup>	Total <sup>c</sup> Yield/%
1	<b>a</b>	125 W, 64.5 h	0.03	2	5	1(3)	4(8)	27(59)	–	–	70
2	<b>b</b>	125 W, 70 h	0.03	2	5	9(18)	–	27(51)	–	–	69
3	<b>c</b>	125 W, 64.5 h	0.03	2	5	–	4(12)	21(64)	–	–	76
4	<b>a</b>	400 W, 6 h	0.03	2	5	1(2)	14(27)	19(38)	13(24)	–	91
5	<b>a</b>	400 W, 12 h	0.13	2	5	11(21)	6(11)	29(54)	1(3)	–	89
6	<b>a</b>	400 W, 12 h <sup>a</sup>	0.13	5	5	18(20)	21(22)	30(33)	3(3)	3(4)	82
7	<b>a</b>	400 W, 12 h <sup>a</sup>	0.13	5	10	2(4)	11(17)	37(57)	–	4(6)	84

<sup>a</sup>In the presence of 5 equiv. of PhCOPh. <sup>b</sup>Yields in brackets are based on recovered **8a-c**. <sup>c</sup>Total yield based on recovered **8a-c**.

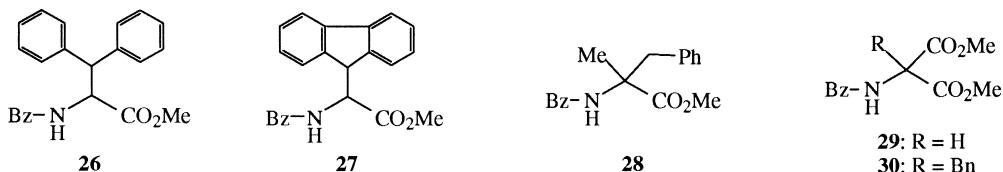
The reaction of toluene with alternative glycine derivatives, namely **14** and **16**, was also explored using the optimum alkylation conditions developed for the formation of **11a**. Hence, reaction of **14** resulted in the formation of **15** in 28% yield (or 62% yield based on recovered **14**) as a 1:1 mixture of diastereomers, while reaction of diketopiperazine **16** gave **17** in 29% yield. The reaction of **16** also produced a small amount of dialkylation (8%) to give **18** as a 1:1 mixture of diastereomers.



Having established the alkylation of glycine derivatives using toluene, a variety of substituted toluenes were then reacted with **8a** under the same conditions. This allowed the formation of phenylalanines **19–25** in 12–36% isolated yield or 35–87% yield based on recovered **8a**.

Although a variety of substituents could be introduced on the benzene ring, the reaction proved to be very sensitive to variation of the (toluene) methyl group. When substituents were introduced at this site the yields of alkylation decreased and, for example, reaction of **8a** with

diphenylmethane or fluorene, produced **26** or **27** in 10 and 8% yield, respectively. This could be a consequence of  $^t\text{BuO}\cdot$  preferentially reacting with the weaker (benzylic) C–H bonds in diphenylmethane and fluorene (compared to toluene) resulting in a low concentration of the captodative radical (derived from **8a**).



In all reactions, no products derived from dialkylation of glycine **8a** were observed. Indeed, attempts to alkylate alanine **10a** or phenylalanine **11a** by photolysis with toluene/peroxide resulted in typically  $\leq 1\%$  yield of dialkylated product **28**. Similarly, the presence of a second ester served to hinder the alkylation of malonate **29** and photolysis in the presence of di-*tert*-butyl peroxide (2 equiv.) and toluene (5 equiv.) produced **30** in 13% yield (or 58% yield based on recovered **29**). The reaction also produced a small amount (3%) of phenylalanine **11a**, presumably derived from photo-decarboxylation of **30**.

This work has demonstrated that a variety of glycine derivatives can be alkylated to form phenylalanines, on photolysis in the presence of substituted toluenes. Whereas related anionic alkylations are often complicated by polyalkylation, this mild free radical method of alkylation allows the selective formation of monoalkylated products.

## Acknowledgements

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7. All new compounds exhibited satisfactory spectral and analytical (high resolution mass) data.
8. There was no evidence for benzylic radical formation on photolysis of related amines, e.g. PhNHCbz or  $^t\text{BuNHCbz}$  (under similar conditions).
9. Alternative photosensitisers, such as 4,4'-dimethoxybenzophenone, were less effective.
10. Photolysis of *N*-acetylglycine methyl ester with benzophenone or 4,4'-dimethoxybenzophenone gave the tertiary alcohol in much lower yield (i.e. 7.7 and 6.4% yield, respectively). Deseke, E.; Nakatani, Y.; Ourisson, G. *Eur. J. Org. Chem.* **1998**, 243–251.