Pergamon

Tetrahedron Letters 42 (2001) 3519–3522

TETRAHEDRON LETTERS

The Barton radical decarboxylation on solid phase. A versatile synthesis of peptides containing modified amino acids

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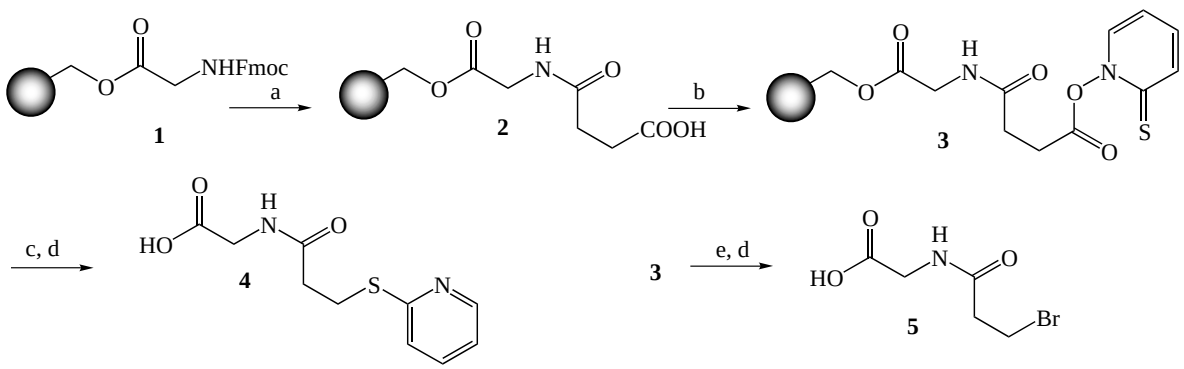
Received 23 February 2001; revised 15 March 2001; accepted 21 March 2001

Abstract—Barton esters were prepared starting from different carboxylic acids loaded on a Wang resin. Light induced fragmentation occurred giving a radical that reacted with $CBrCl_3$ to give the corresponding bromides, whereas conjugate addition to electron-poor alkenes proved to be less synthetically useful. The bromides so formed were further functionalised on the resin with different nucleophiles. © 2001 Elsevier Science Ltd. All rights reserved.

The development of organic synthesis on solid support is important for the preparation of libraries of products for the discovery of new bioactive compounds, new catalysts or new materials. Therefore a considerable number of organic reactions have been successfully applied on solid phase.[1] On the other hand, although extensively employed in solution,[2] radical reactions have not been widely applied on solid supports. Some examples of radical cyclisations[3] and intermolecular conjugate additions to radical acceptors anchored to polymer supports[4] have been recently described.

In a recent publication, we reported the use of the Barton ester derived from protected glutamic acids in the synthesis of exotic amino acids.[5] In this case the introduction of different functionalities in the side chain of the amino acid required the use of a large excess of radical acceptor and the final products had to be purified by column chromatography from the 2-pyridinethione by-products. Expecting that these limits could be overcome on solid phase, we decided to attempt the photochemical decarboxylation of a Barton ester loaded on a solid support and investigate its application to the synthesis of peptides containing modified amino acids.

To find the correct reaction conditions, we prepared first a Barton ester on solid phase and then generated a radical by irradiation of the resin with an ordinary tungsten lamp. As a model, a Wang type resin was



Scheme 1. (a) 25% Piperidine in DMF, 25 min followed by succinic anhydride, DMF (3 equiv.), 70°C, 3 h. (b) 1-Hydroxy-2-pyridinethione (3 equiv.), HBTU (3 equiv.), DIPEA (4 equiv.), DMF, rt, 4 h. (c) hν (200 W lamp), THF, 20 min. (d) $TFA/CH_2Cl_2/Et_3SiH$ (1/1/0.1), rt, 1 h. (e) hν (200 W lamp), $CBrCl_3$ (50 equiv.), DMF, 20 min.

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PII: S0040-4039(01)00496-8

loaded with Fmoc-Gly-OH and, after deprotection of the nitrogen, reacted with succinic anhydride to give product **2** (Scheme 1). The correct loading was monitored with a negative Kaiser's test[6] and with a positive Malachite Green test[7] which confirmed the presence of a free COOH on the resin.

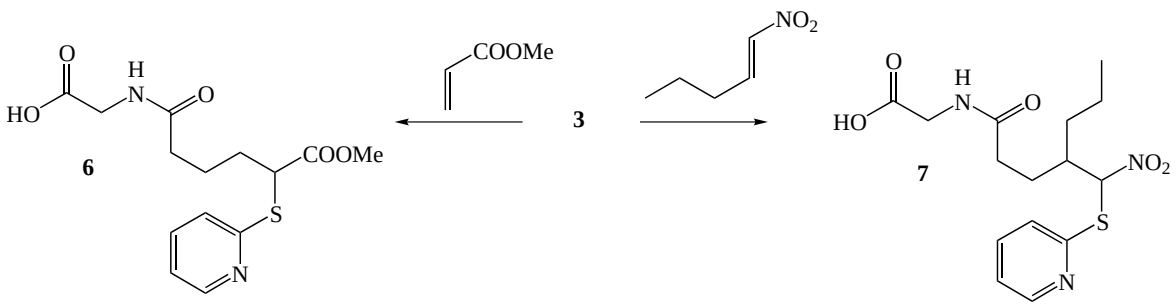
The Barton ester **3** was prepared by reaction of **2** with 1-hydroxy-2-pyridinethione using HBTU (2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) in the presence of DIPEA in DMF.[8] The complete formation of **3** was monitored again with a negative Malachite Green test. Irradiation of **3** in benzene or THF followed by acid cleavage gave product **4** in 76% isolated yield.

As the formation of compound **4** proved the successful fragmentation of the Barton ester, we tried to irradiate **3** in the presence of $CBrCl_3$. When the reaction was carried out in THF or using $CBrCl_3$ as the solvent, we obtained, after cleavage from the resin, a mixture of compounds **4** and **5**. When the irradiation was carried out in DMF in the presence of at least 50 equiv. of $CBrCl_3$, compound **5** was obtained exclusively in 72% yield.

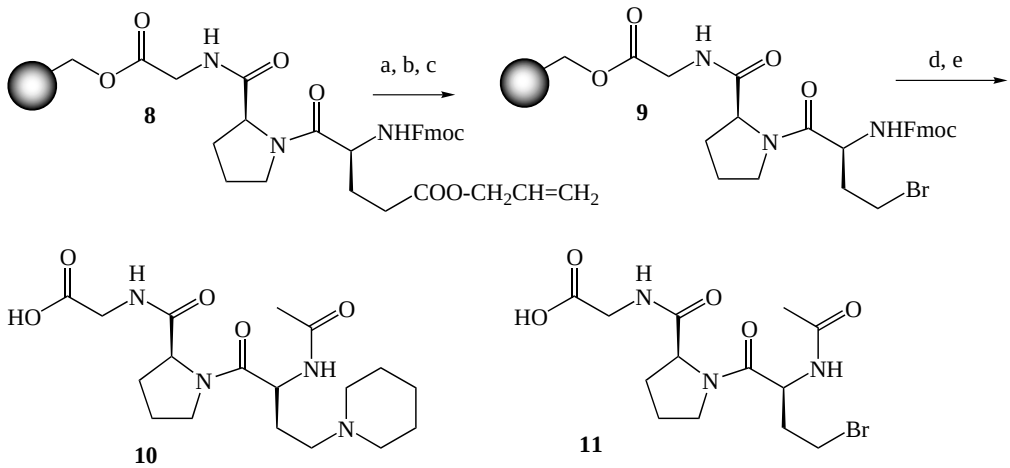
The Barton ester **3** was also reacted with electron-poor alkenes such as methyl acrylate or 1-nitro-1-pentene.[9] When the reaction was carried out in DMF with 50 equiv. of the radical acceptor, the main reaction product was compound **4**. The expected products of regioselective addition of the $R^{\bullet}$ and $ArS^{\bullet}$ across the double bond (compounds **6** and **7** in Scheme 2) were obtained using more that 100 equiv. of the electron poor alkenes in DMF. In any case, 10–20% of product **4** was always obtained.

As the reaction that seemed to be synthetically more useful was the quenching of the radical with $Br^{\bullet}$, we tried to apply it to the solid phase synthesis of modified peptides. Thus tripeptide **8** was prepared on a Wang resin coupling, in sequence,[10] Fmoc-Gly-OH, Fmoc-Pro-OH and Fmoc-Glu-OH protected at the γ-carboxylic group as an allyl ester.[11] After deprotection of **8** with $Pd(PPh_3)_4$,[12] the free COOH was transformed into the Barton ester following the standard procedure (Scheme 3).

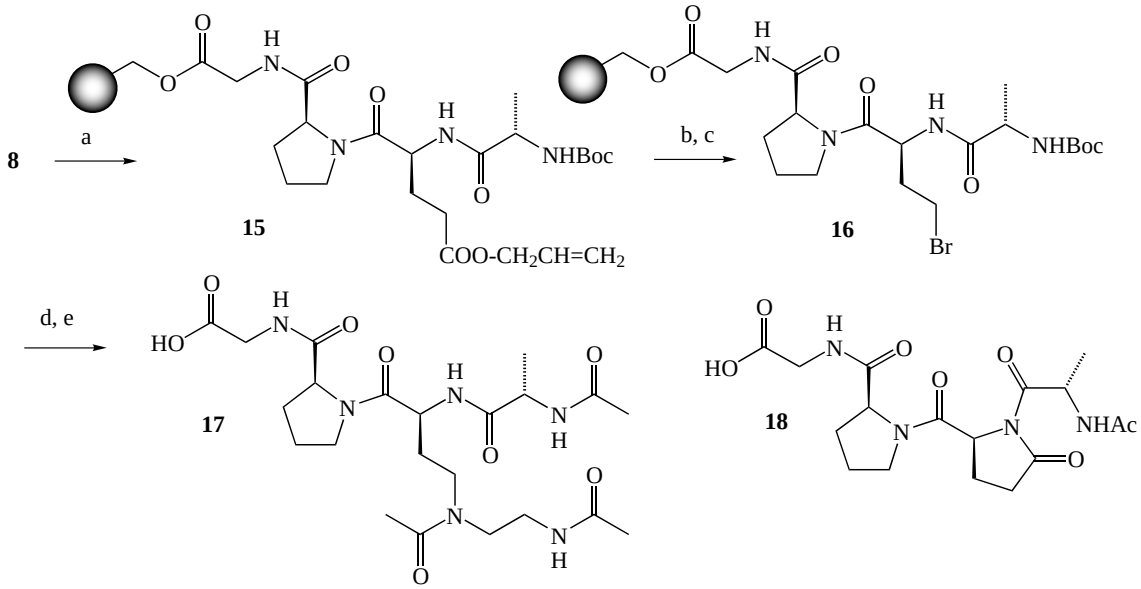
Irradiation in the presence of $CBrCl_3$ in DMF gave compound **9** which was then treated with 25% piperidine in DMF for 20 min to deprotect the nitrogen. As **9** might undergo nucleophilic substitution of the bromine with piperidine, we quenched the resin after deprotection with Ac_2O and cleaved the reaction products. A mixture of compound **10** together with 20–30% of the corresponding *N*-acetyl bromoderivative **11** was



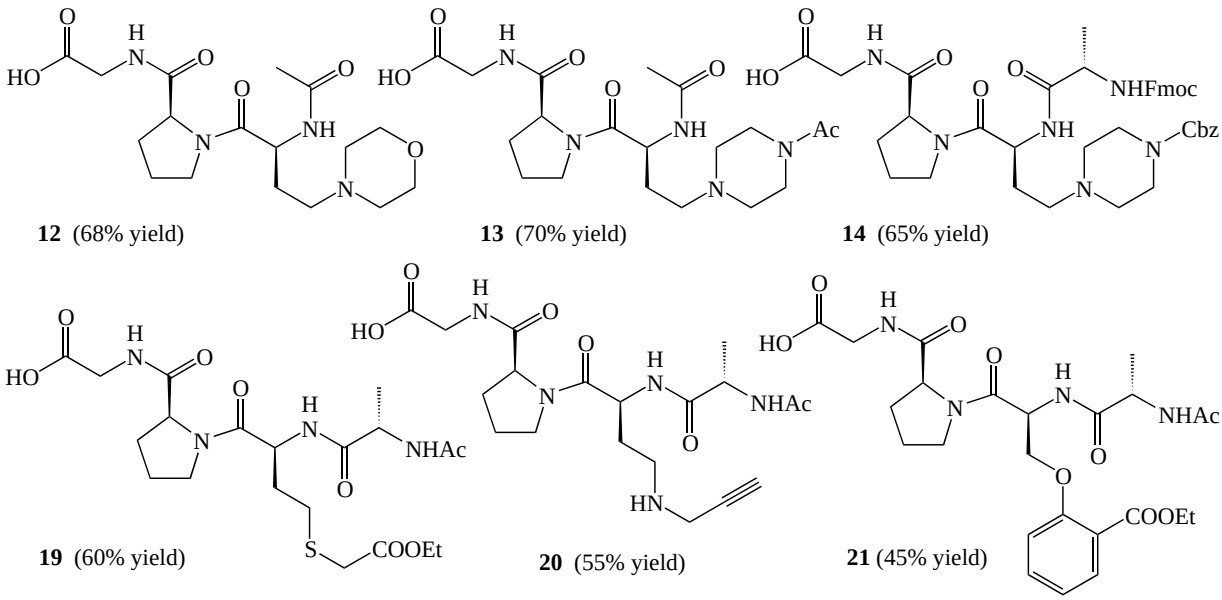
Scheme 2.



Scheme 3. (a) $Pd(PPh_3)_4$ (3 equiv.) $CHCl_3$/AcOH/NMM (37/2/1) rt, 2 h. (b) 1-Hydroxy-2-pyridinethione (3 equiv.), HBTU (3 equiv.), DIPEA (4 equiv.), DMF, rt, 4 h. (c) hν (200 W lamp), $CBrCl_3$, DMF, rt, 40 min. (d) 25% Piperidine, DMF, 3 h. (e) Ac_2O, DIPEA, DMF, 30 min followed by TFA/CH_2Cl_2/Et_3SiH (1/1/0.1), rt, 1 h.



Scheme 4. (a) 25% Piperidine in DMF followed by *N*-Boc-Ala-OH (2 equiv.), DMTMM (2 equiv.), NMM (4 equiv.) in NMP. (b) $Pd(PPh_3)_4$ (3 equiv.) $CHCl_3$/AcOH/NMM (37/2/1) rt, 2 h. (c) 1-Hydroxy-2-pyridinethione (3 equiv.), DMTMM (3 equiv.), NMM (4 equiv.), NMP rt, 1 h, followed by hν (200 W lamp), $CBrCl_3$, DMF, rt, 40 min. (d) $BocHNCH_2CH_2NH_2$ (2 equiv.), NMM (2 equiv.), DMF, 3 h. (e) TFA/CH_2Cl_2/Et_3SiH (1/1/0.1) rt, 1 h then Ac_2O, DIPEA, THF, 30 min.



Scheme 5.

obtained. The reaction of **9** with 25% piperidine in DMF for 3 h, followed by quenching with Ac_2O and cleavage from the resin, gave exclusively, compound **10** in 75% yield. Similar reactions were carried out using solutions of morpholine or piperazine to give compounds **12** and **13** (Scheme 5) in about 70% yield. When 4-Cbz-piperazine was used (10 equiv. in DMF), followed by coupling of the free NH_2 with *N*-Fmoc-alanine and cleavage from the resin, we obtained compound **14** in 65% yield. Compound **14** (Scheme 5) is a modified peptide having two amines protected in such a way that orthogonal elongation of the structure is possible.

To realise a more versatile approach to the synthesis of modified peptides, we carried out the photochemical radical decarboxylation after deprotection of the Fmoc group and further coupling with an *N*-Boc protected amino acid. Thus treatment of **8** with piperidine in DMF followed by reaction with *N*-Boc-Ala-OH in the presence of DMTMM as the coupling agent gave product **15**. Deprotection of the allyl ester was accomplished with $Pd(PPh_3)_4$ to give the acid (positive Malachite Green test and FT-IR analysis of the beads). The Barton ester was prepared using HBTU as the coupling agent followed by reaction with $BrCCl_3$ in DMF under photoirradiation to give bromide **16**. Nucleophilic

substitution of the bromide with 1-*N*-Boc-ethylenediamine was carried out in DMF in the presence of DIPEA. After cleavage from the resin, the crude reaction mixture was treated with Ac_2O in order to obtain a product soluble in organic solvents. The analysis of the mixture showed that the expected compound **17** was formed together with at least 20% of the lactam **18** produced by intramolecular cyclisation of the activated carboxylate used in the synthesis of the Barton ester. We explored the use of different coupling agents to minimise the formation of **18**. However, it was found that on using PyBOP or DMTMM in NMP for the preparation of the Barton ester, the required compound **17** was formed in less than 10% yield. Starting with 300 mg of a Wang resin with a loading of 1.4 mmol/g, we obtained, after cleavage, about 140 mg of crude product from which compound **18** was isolated in 51% yield (109 mg) (Scheme 4).

When bromide **16** was reacted with different nucleophiles (such as $HSCH_2COOEt$, propargylamine or ethyl salicylate in DMF and in the presence of NMM) products **19**–**21** were obtained after cleavage and short column chromatography (to separate from **17**) in the yields reported in Scheme 5.

In conclusion, we have demonstrated that the photochemical fragmentation of the Barton ester can be successfully employed to generate a radical on solid phase. The reaction was employed to generate peptides containing exotic amino acids on solid phase. An intermolecular version of this reaction and its application to the preparation of libraries is currently underway in our laboratories and will be reported in due course.

Acknowledgements

This work was supported by grants from the University of Sassari (Fondi ex-60%).

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