Generation of 1-Amidoalkyl Radicals from N-Protected Amino Acids: An Alternative to the Barton Decarboxylation Procedure

Aleksandar Stojanovic and Philippe Renaud*

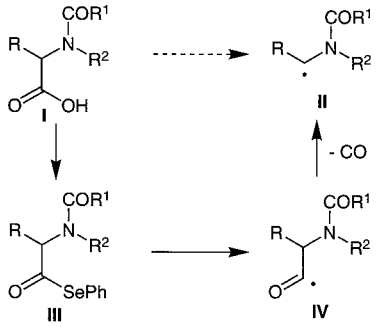
Université de Fribourg, Institut de Chimie Organique, Pérolles, CH-1700 Fribourg (Switzerland)

Fax: 41 26 300 87 77; E-mail: philippe.renaud@unifr.ch

Received 25 October 1996

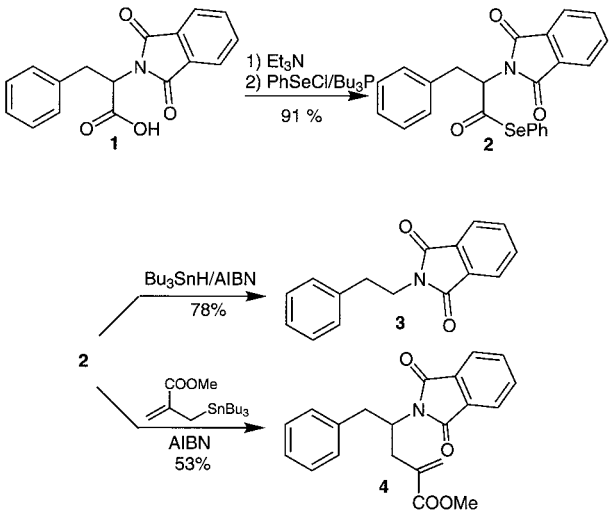
Abstract: An alternative method to the Barton decarboxylation procedure of N-protected amino acids is presented. The carboxylic acids are transformed into stable phenylselenoesters. Upon standard radical reaction conditions, they generate acyl radicals which undergo a very fast decarbonylation reaction to N-protected 1-aminoalkyl radicals. The decarbonylated radicals are trapped reductively and by intermolecular additions to olefins.

1-Amidoalkyl radicals are interesting reactive intermediates which have been recently applied to the synthesis of numerous biologically active compounds such as rare amino acids and alkaloids.[1] An obvious way to generate them is the decarboxylation of N-protected amino acids (**I** → **II**). Attempts to use the electrochemical decarboxylation lead mainly to overoxidation of the radicals to the iminium ions (Hofer-Moest reactions).[2] A more successful approach was developed by Barton based on the decarboxylation of thiohydroxamic esters.[3] This procedure gave satisfactory results, however, the intermediate thiohydroxamates (the so-called "Barton ester") are difficult to purify and cannot be stored because of their instability. Moreover, their use for C,C-bond formation is limited by the rearrangement reaction leading to N,S-pyridyl acetals. We report here a new preparative method based on the decarbonylation of selenoesters of type **III**. The intermediate acyl radical **IV** is expected to decarbonylate easily to the more stable 1-amidoalkyl radical **II**.[4-6]

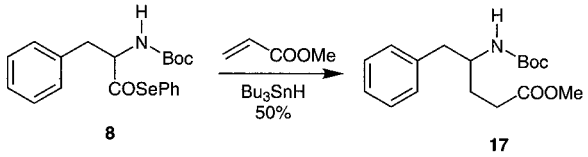


A preliminary study was run starting from N-phthaloylphenylalanine **1**.[7] The phenylselenoester **2** was prepared by adding the triethylammonium salt of **1** to a solution of PhSeCl/Bu_3P in THF (procedure A).[8] After 3 h, the reaction was complete and the stable selenoester **2** was purified by chromatography. Radical reduction of **2** with Bu_3SnH (1.5 equiv)/AIBN in C_6H_6 gave the phthalimide **3** in 78 % yield. The decarbonylation is fast and does not require a slow addition of Bu_3SnH. No trace of the amino aldehyde could be detected in the crude mixture. Interestingly, allylation using [2-(methoxycarbonyl)]propenyltributylstannane was successful and gave **4** in 53 % yield. This is, to our knowledge, the first example of C,C-bond formation using a 1-amidoalkyl radical generated by decarbonylation of an acyl radical.

The scope and limitations of the method were investigated by preparing selenoesters starting from the different protected amino acids **5-7** (Table). The preparation of the selenoester from the N-Boc-phenylalanine **5** according to procedure A[8] (Et_3N followed by PhSeCl/Bu_3P) was not possible presumably because of concurrent deprotection. This problem was easily solved by using procedure B:[4a] the carboxylic acid was transformed into a mixed anhydride (N-methylmorpholine/*i*-BuOCOCl) and treated with sodium phenylseleno(triethoxy)borate (prepared from PhSeSePh and $NaBH_4$ in ethanol).[9] The selenoester **8** was isolated in 81 % yield. The phenylselenoesters **9** and **10** have been prepared according to procedure A with satisfactory yields.[10] The reduction of the selenoesters **8-10** with Bu_3SnH/AIBN gave the corresponding decarboxylated protected amines **11-13** in good to excellent yields (> 75 %).[11] The allylation reactions were also possible in all three cases and gave products **14-16** in satisfactory yields (see Table).[12] It is of interest to note that this method is very efficient for the generation of 1-amidoalkyl radicals having a hydrogen substituent on the nitrogen atom (see selenoester **8**). These radicals are difficult to generate from N,X-acetal (X = halide, SR, SeR) because of the instability of the radical precursors.



Finally we have investigated the classical radical addition to methyl acrylate mediated by Bu_3SnH starting from the selenoester **8**.[13] The addition product **17** was isolated in 50% yield (unoptimized).[14] This reaction therefore represents a useful homologation of an α-amino acid by two carbon atoms leading to a γ-amino acid derivative. We are actually developing a similar reaction sequence with retention of the absolute configuration.



In conclusion, we have demonstrated here that decarbonylation of acyl radicals derived from amino acids via their phenylselenoesters is a valuable and general method for the reductive decarboxylation of amino acids. Moreover, the transient 1-amido substituted radicals can be used for intermolecular C,C-bond forming reactions. Due to the diversity of naturally occurring and synthetic amino acids, we expect that this method will become an important alternative to other existing methods for the generation of 1-amidoalkyl radicals.

Acknowledgment. We are very grateful to the Swiss National Science Foundation (Project 20-44'234.95) for funding and to Ciba-Geigy AG (Marly) for performing the microanalyses.

References and Notes:

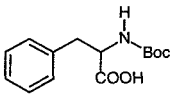
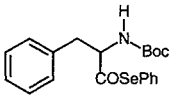
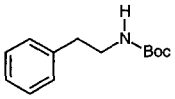
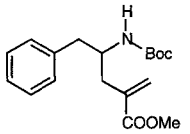
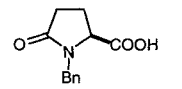
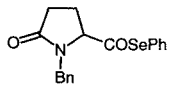
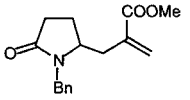
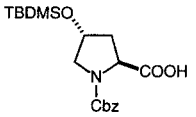
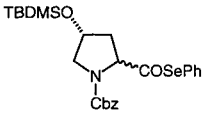
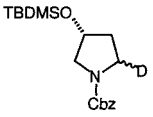
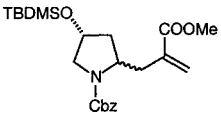
(1) For a recent review, see: Renaud, P.; Giraud, L. *Synthesis* **1996**, 913-926.

(2) Linstead, R. R.; Shepard, B. R.; Weedon, B. C. L. *J. Chem. Soc.* **1951**, 2854-2859.

(3) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479-5486.

(4) The decarbonylation of acyl radicals derived from the selenoesters

Table. Decarboxylative reduction and Allylation of N-protected amino acids **5-7** via their selenoesters **8-10**.

Amino Acid	Selenoester[a] (yield, method)	Reduction product[11] (yield)	Alkylation product[12] (yield)
 **5**	 **8** (81%, B)	 **11** (90%)	 **14** (58%)
 **6**	 **9** (60%, A)	 **12** (91%)	 **15** (62%)
 **7**	 **10** (79%, A)	 **13**[b] (79%, *trans/cis* 1:1)	 **16** (69%, *trans/cis* 1.7:1)

a) Procedure A: Et_3N (r.t., 10 min), then PhSeCl/Bu_3P (r.t., 3 h).[8] Procedure B: N-methylmorpholine/*i*-BuOCOCl (-15 °C, 30 min), then SeSePh/$NaBH_4$ (-15 to 0 °C, 1 h).[4a]
b) Bu_3SnD was used instead of Bu_3SnH.

of N-protected amino acids has already been observed but never investigated for its synthetic potential: (a) Crich, D.; Eustace, K. A.; Ritchie, T. J. *Heterocycles* **1989**, *28*, 67-70. (b) Boger, D.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429-1443. During the writing of this manuscript, we became aware of a study of the decarbonylation of selenoesters derived from N-alkylated amino acids: (c) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett*, **1997**, ??.

(5) The reduction of α-oxygenated phenylselenoesters with tributyltin hydride is known to give decarbonylated products: Ireland, R.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285-3294. For other radical decarbonylations of phenylselenoesters, see: Pfenninger, J.; Heuberger, C.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 2328-2337. Pfenninger, J.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 1563-1581.

(6) For some rate constants of decarbonylation of acyl radicals, see: Fischer, H.; Henning, P. *Acc. Chem. Res.* **1987**, *20*, 200-206.

(7) Phthalimido substituted radicals have been shown to be unique for the control of the diastereoselectivity in acyclic systems: Damm, W.; Hoffmann, U.; Macko, L.; Neuburger, M.; Zehnder, M.; Giese, B. *Tetrahedron* **1994**, *50*, 7029-7048. Renaud, P.; Stojanovic, A. *Tetrahedron Lett.* **1996**, *37*, 2569-2572.

(8) Batty, D.; Crich, D. *Synthesis* **1990**, 273-275.

(9) Miyashita, M.; Hoshino, H.; Yoshikoshi, A. *Tetrahedron Lett.* **1988**, *29*, 347-350. Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697-2699.

(10) Epimerization of the α-center was observed during the formation of the selenoester **10**.

(11) General procedure for the formation of **11-13** from selenoesters **8-10**. A degassed soln. of the selenoester **8**, **9** or **10** (0.50 mmol), Bu_3SnH (218 mg, 0.75 mmol) and AIBN (13 mg, 0.08 mmol) in benzene (4 ml) was irradiated with a 300 W sun lamp under N_2 at 10 °C for 2 h. A sat. aq. KF soln. was added and the mixture was stirred for 1 h at r.t.. After extraction with Et_2O, the crude product was purified by flash chromatography. Physical and spectral data of **11-13** were in good accordance with literature data: **11**: Tanaka, K.-I.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1988**, *36*, 3125-3129. **12**: commercially available (Aldrich 12,375-7). **13**: Trybulski, E. J.; Krammss, R. H.; Brabander, H. J. to *American Cyanamid Co.*, Eur. Pat. 92-103491.

(12) Typical procedure for the formation of **14-16**. A degassed solution of the selenoester **8**, **9** or **10** (0.50 mmol), [2-(methoxycarbonyl)propenyl]tributylstannane (389 mg, 1.00 mmol) and AIBN (16 mg, 0.10 mmol) in benzene (4 ml) was brought to reflux under N_2 for 3 h. A sat. aq. KF soln. was added and the mixture was stirred for 1 h at r.t.. After extraction with Et_2O, the crude product was purified by flash chromatography. ^{1}H-NMR (360 MHz): **14** ($CDCl_3$): 7.32-7.18 (*m*, 5 arom. H); 6.21 (*d*, *J* = 1.1, C=C*H*H); 5.59-5.58 (*m*, C=CH*H*); 3.74 (*s*, COOMe); 4.49 (*br. d*, *J* = 8.0, NH); 3.96-3.74 (*br. m*, CH-N); 2.88 (*dd*, *J* = 13.4, 6.6, PhCH*H*); 2.77 (*dd*, *J* = 13.4, 6.8, PhC*H*H); 2.55 (*dd*, *J* = 14.0, 4.0, *H*HC-C=C); 2.31 (*dd*, *J* = 14.0, 10.3, H*H*C-C=C); 1.37 (*s*, *t*-Bu). **15** ($CDCl_3$): 7.32-7.22 (*m*, 5 arom. H); 6.22 (*d*, *J* = 1.1, C=C*H*H); 5.55 (*s*, C=CH*H*); 4.96 (*d*, J_{AB} = 14.8, PhCH*H*, part of AB); 4.03 (*d*, J_{AB} = 14.8, PhC*H*H, part of AB); 3.68-3.55 (*m*, CH-N); 3.67 (*s*, COOMe); 2.82 (*dd*, *J* = 13.4, 2.9, *H*HC-C=C); 2.52-2.42 (*m*, H*H*C-C=C); 2.34 (*ddd*, *J* = 17.1, 9.7, 5.1, C*H*H-CO); 2.15 (*dd*, *J* = 13.4, 9.7, CH*H*-CO); 2.01-1.90 (*m*, C*H*H-CH_2-CO); 1.73-1.69 (*m*, CH*H*-CH_2-CO). **16** (DMSO-d_6, 80 °C, major isomer): 7.60-7.22 (*m*, 5 arom. H); 6.01 (*d*, J = 1.3, C=C*H*H); 5.51 (*s*, C=CH*H*); 5.05 (*d*, J_{AB} = 12.9, PhC*H*H, part of AB); 5.01 (*d*, J_{AB} = 12.6, PhCH*H*, part of AB); 4.40-4.35 (*m*, CH-O); 4.13-4.05 (*m*, CH-N); 3.61 (*s*, COOMe); 3.49-3.30 (*m*, CH_2-N); 2.69 (*ddd*, *J* = 14.1, 5.2, 1.0, C*H*H-C=C); 2.39 (*ddd*, *J* = 13.7, 8.0, 0.9, CH*H*C-C=C); 1.86-1.73 (*m*, CH_2CHN); 0.81 (*s*, *t*-Bu); 0.01 and 0.00 (2 *s*, 2 Me).

(13) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 553-579.

(14) A degassed soln. of **8** (404 mg, 1.00 mmol), methyl acrylate (0.90 ml, 10.0 mmol) and AIBN (5 mg, 0.03 mmol) in benzene (10 ml) was brought to reflux under N_2. A soln. of Bu_3SnH (437 mg, 1.50 mmol) and AIBN (20 mg, 0.12 mmol) in benzene (15 ml) was added over a period of 12 h using a syringe pump. The reaction mixture was refluxed for 1 h and then cooled to r.t.. A sat. aq. KF soln. was added and the mixture was stirred for 1 h at r.t.. After extraction with Et_2O, purification of the crude product by flash chromatography gave **17** (150 mg, 50 %) as a white solid. ^{1}H-NMR (360 MHz): 7.31-7.17 (*m*, 5 arom. H); 4.36 (*br. d*, *J* = 9.1, NH); 3.89-3.77 (*m*, CH-N); 3.65 (*s*, COOMe); 2.83 (*dd*, *J* = 13.4, 5.7, PhC*H*H); 2.73 (*dd*, *J* = 13.4, 6.8, PhCH*H*); 2.45-2.30 (*m*, 2 H, CH_2COOMe); 1.93-1.81 (*m*, CH*H*-CH_2-COOMe); 1.67-1.56 (*m*, C*H*H-CH_2-COOMe); 1.40 (*s*, *t*-Bu).