A Novel Synthesis of Peptides Based on the Photochemistry of 5-Azido-1,3,4-oxadiazoles

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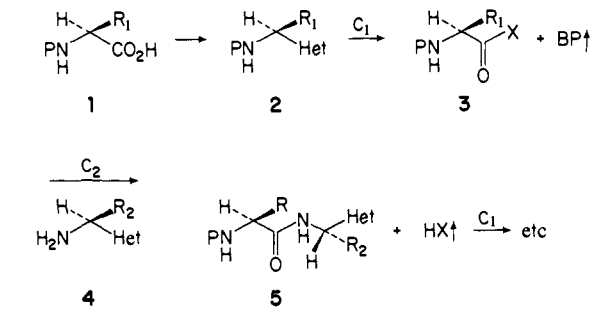
Abstract: A novel approach to the synthesis of peptides is described. Various N-protected amino acid hydrazides **17** were converted to the salts **18** by condensation with carbon disulfide in methanolic potassium hydroxide. Thermal cyclization of **18** to the heterocycles **19** was followed by reaction with methyl iodide to yield the sulfides **20**. After oxidation of **20** to the corresponding sulfones **21**, the title compounds **22** were prepared by treating **21** with sodium azide. Deprotection then yielded the free bases **23**. Utilization of **22** and **23** in peptide synthesis, relying on a photochemical degradation of the title heterocycle present in these compounds, is described. The scope and limitations of this new methodology are also discussed.

A conceptually novel approach to the synthesis of peptides, amenable in principle to automation in a "peptide synthesizer", is outlined in Scheme I.[3] The carboxyl function of a suitably protected amino acid **1** is converted to a specific heterocycle to give a species of general structure **2**. The choice of that heterocycle is dictated by a number of particular chemical properties it must possess. Under a set of reaction conditions C_1, the heterocycle must reorganize to yield an activated ester **3**, suitable for a peptide coupling operation. An additional requirement is that all by-products (BP) from this process as well as any reagents involved in C_1 be gaseous and therefore not accumulate in the sequence. Since under reaction conditions C_2 the coupling of **3** with the amino heterocycle **4** to yield the dipeptide derivative **5** produces HX, a further demand must be placed on the nature of X also. Therefore, X is limited to those leaving groups whose conjugate acid HX is a gas as well. Utilization of the above cycle then allows the elongation of the peptide chain with the production of only gaseous byproducts, thus eliminating the need for isolation and purification at each step. We report preliminary results which demonstrate the feasibility of such an approach.

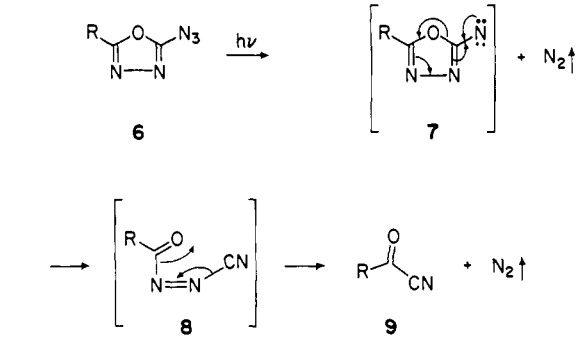
A candidate for the heterocycle described in Scheme I that theoretically meets all requirements is a 2-substituted 5-azido-1,3,4-oxadiazole **6** (Scheme II).[4] Such an aggregate is expected to be photolabile, affording a transient nitrene **7**[5] under reaction conditions $C_1 = h\nu$ along with an equivalent of nitrogen. The reactive species **7** should rearrange to produce the azo intermediate **8** which in principle can expel a second mole of nitrogen to yield the acyl cyanide **9**, an example of species **3** with X = CN. Of course this satisfies the requirement that HX = HCN be gaseous as outlined above.[6,7]

A single example of **6** (R = Ph) had in fact been reported by Stollé.[8] Although his synthesis of **6** included conditions not suitable for our peptide application, we nonetheless prepared a sample of **6** (R = Ph) by modifications of his methodology and photolyzed the final product. Gas evolution was observed and the singular photoproduct was benzoyl cyanide **9** (R = Ph),[6a] fulfilling all expectations.[9]

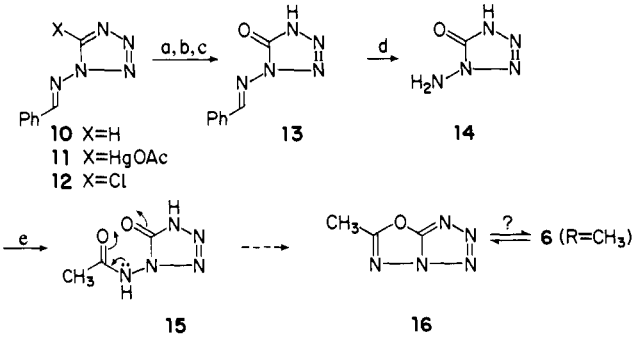
Scheme I



Scheme II



Scheme III



[a] $Hg(OAc)_2$, 95% $EtOH/H_2O/HOAc$, 70:40:**1**, Δ, 5 min (99%). [b] Cl_2, acetone, 25 °C, 2 h, (76%). [c] 1 N NaOH, 95% $EtOH/H_2O$, 3:2, Δ, 2 h, (82%). [d] Concentrated HCl/H_2O, 2:1, Δ, 0.75 h. [e] Ac_2O, TFA (cat), Δ, 1 h, (83%).

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(2) Deceased July 8, 1979.

(3) For leading references on Modern Methods of Peptide Synthesis, see: Pettit, G. R. "Synthetic Peptides"; Elsevier: New York, 1980; Vol. 5. Gross, E., Meienhofer, J. "The Peptides, Special Methods in Peptide Synthesis, Part A"; Academic Press: New York, 1980.

(4) The first known synthesis of this class of heterocycles was the preparation of 2-benzyl-4-phenyl-1,3,4-oxadiazol-5-one by Freund and Goldsmith (Freund, M.; Goldsmith, B. B. *Chem. Ber.* **1888**, *21*, 1240, 2456). For a review, see: Boyer, J. H. *Heterocycl. Compd.* **1961**, *7*.

(5) L'abbé, G. *Chem. Rev.* **1969**, 345.

(6) (a) An efficient synthesis of aroyl cyanides has recently been described: Tanaka, M.; Koyanagi, M. *Synthesis* **1981**, *12*, 972-974. See also: Thesing, J.; Witzel, D.; Brehm, A. *Angew. Chem.* **1956**, *68*, 425 and leading references therein. (b) Buu-Hoi; Gagniant, P. *Zh. Obshch. Khim.* **1951**, *21*, 694; *Chem. Abstr.* **1951**, *45*, 9020.

(7) Dipeptides have actually been prepared by converting Phth-Gly-Br to Phth-Gly-CN by using prolonged fusion with cuprous cyanide and then coupling the latter with amino acids. Kenner, G. W.; Jones, D. S.; Sheppard, R. C. *J. Chem. Soc.* **1965**, 4393.

(8) Stollé, R.; Fehrenbach, K. *J. Prakt. Chem.* **1929**, *122*, 289.

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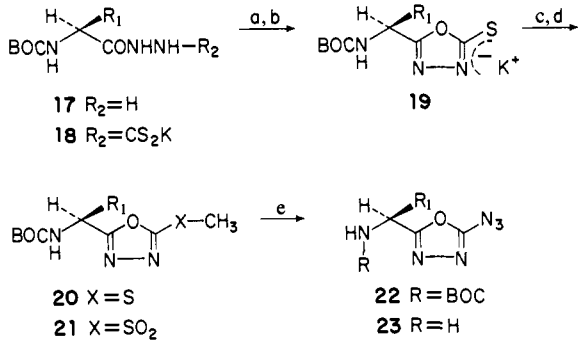
Scheme IV

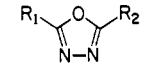


[a] CS_2, KOH, 95% EtOH, 25 °C, 1 h. [b] 95% EtOH, Δ, 5 h. [c] 95% EtOH, CH_3I, Δ, 0.25. [d] $KMnO_4$, $HOAc/H_2O$, 1:3, 25 °C, 2 h. [e] 95% EtOH, NaN_3, Δ, 0.5 h.

Since an alternate synthesis of 5-azido-1,3,4-oxadiazoles was required, we prepared the aminotetrazolone **14** as a reagent which potentially could serve this purpose as outlined in Scheme III. The known tetrazole **10**[10] was converted to its mercury derivative **11** which smoothly reacted with elemental chlorine to afford the chlorotetrazole **12**.[11] This was saponified to the protected tetrazolone **13**, and the Schiff base was hydrolyzed to yield the desired 1-aminotetrazolone (**14**). Acylation at the amino substituent was effected[12] and a dehydrative cyclization of the resulting model acetamide **15** to the hybrid bicycle **16** was studied. This hybrid species was expected to tautomerize to the targeted 5-azido-1,3,4-oxadiazole system in accordance with precedents regarding the imino azide/tetrazole equilibrium.[13] This final transformation was still under study when the following alternate approach proved successful.

Reaction of *N*-Boc amino acid hydrazides **17** with carbon disulfide in ethanolic potassium hydroxide yielded the salts **18** (Scheme IV).[14] These compounds were found to cyclize upon heating to afford the ambident anions **19** which were alkylated solely at sulfur by quenching with methyl iodide.[15] The resulting sulfides **20** were oxidized to the sulfones **21** which underwent a facile addition–elimination reaction with sodium azide to yield the azidooxadiazoles **22**, examples of species **2** (Scheme I).[16]

Table I



cmpd	R_1	R_2	mp,[a] °C	yield,[e]
27	*p*-nitrophenyl	SCH_3	158–160	83
28	$TsNHCH_2$	SCH_3	116–117	100
29	$PhCH_2$	SCH_3	65–65	94
30	$BocNHCHCH_2Ph$	SCH_3	126–127	95
31	$BocNHCHCH_3$	SCH_3	oil	95
32	$Boc\text{-}Gly\text{-}NHCHCH_2Ph$	SCH_3	100–102	74
33	1-naphthyl	SCH_3	45–50[b]	71
34	*n*-undecyl	SCH_3	44–45	98
35	$Cbz\text{-}NHCH_2$	SO_2CH_3	105–106	97
36	$Boc\text{-}Gly\text{-}NHCHCH_2Ph$	SO_2CH_3	123–125	93
37	$Cbz\text{-}Gly\text{-}NHCH_2$	SO_2CH_3	134–136	84
38	1-naphthyl	SO_2CH_3	107–108	96
39	$p\text{-}CH_3OPh$	SO_2CH_3	165–166	95
40	$Boc\text{-}NHCHCH_3$	SO_2CH_3	oil	95
41	$Boc\text{-}NHCHCH_2Ph$	SO_2CH_3	122–123	61
42	*i*-Pr	N_3	oil	90
43	$TsNHCH_2$	N_3	127–128	96
44	$Boc\text{-}NHCH_2$	N_3	oil	95
45	$Boc\text{-}NHCHCH_2Ph$	N_3	115–117	91
46	$Cbz\text{-}NHCH_2$	N_3	108–109	96
47	1-naphthyl	N_3	84–85	100
48	*n*-undecyl	N_3	35–38	99
49	*p*-nitrophenyl	N_3	147–148	99
50	$Cbz\text{-}Gly\text{-}NHCH_2$	N_3	127–128	91
51	$Boc\text{-}Gly\text{-}NHCHCH_2Ph$	N_3	oil	68
52	H_2NCH_2	N_3	67–68[b]	80
53	H_2NCHCH_2Ph	N_3	71–72	100

[a] Recrystallized from $EtOH/H_2O$ unless otherwise noted. [b] Recrystallized from petroleum ether. [c] Recrystallized from EtOAc/petroleum ether. [d] Recrystallized from CH_2Cl_2/petroleum ether. [e] Based on immediate precursor.

Removal of the Boc group with TFA[17] followed by aqueous base produced the desired crystalline, optically active amino derivatives **23**.

Irradiation of 5-azido-2-((tosylamino)methyl)-1,3,4-oxadiazole (**43**, Table I) in a 1:1 benzene/ethanol solution at 25 °C with 375-nm light for 3 h cleanly afforded Ts-Gly-OEt in quantitative yield. The product was identical with an authentic specimen[18] and is presumably formed by ethanolysis of the acyl cyanide intermediate. Further encouragement was obtained by a similar photolysis in methylene chloride of 5-azido-2-(1-naphthyl)-1,3,4-oxadiazole (**47**) to 1-naphthoyl cyanide[6a] which was subsequently reacted with benzylamine to yield 1-naphthoic acid benzamide in 99% overall yield. Similarly, the *n*-undecyl derivative **48** yielded lauryl benzamide in 60% yield. With these ample precedents in hand, we carried out an irradiation of **22** (R_1 = CH_2Ph) in methylene chloride with 375-nm UV light in a Rayonet at 25 °C for 1.75 h, followed by the addition of benzylamine (UV off). This sequence afforded in 65% yield the expected $Boc\text{-}Phe\text{-}NHCH_2Ph$, mp 131–132 °C ($EtOH/H_2O$), identical with a sample prepared by a Curtius azide coupling reaction of $Boc\text{-}Phe\text{-}N_3$ and benzylamine. Alternatively, irradiation of **22** (R_1 = CH_2Ph) followed by reaction with the free amino heterocycle **23** (R_1 = CH_2Ph) yielded the dipeptide derivative **24**, a member of the class represented by **5** (Scheme I), in 57% yield (unoptimized). Photolysis of the glycylphenylalanine-derived azidooxadiazole **25** in methylene chloride in the presence of benzylamine afforded $Boc\text{-}Gly\text{-}Phe\text{-}NHCH_2Ph$, mp 141–142 °C ($EtOH/H_2O$), in 97%

(9) This is in contrast to a reported photodimerization of aroyl cyanides reported by Raaen (Raaen, V. F. *J. Org. Chem.* **1966**, *31*, 3310), which afforded the bis(cyanohydrin) of benzil as the photoproduct in the presence of a triplet sensitizer. The acyl cyanide moiety is photostable under our conditions.

(10) Hagedorn, I.; Winkelmann, H. D. *Chem. Ber.* **1966**, *99*, 850.

(11) All attempts at direct halogenation of **10** lead to extensive degradation. This two-step procedure was readily carried out and yielded **12** in 76% overall yield.

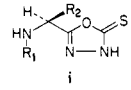
(12) Acylation at oxygen in **14** could be also accomplished by preparation of the silver salt i followed by reaction with an acid chloride to yield ii.

i R=Ag
ii R=R'CO

(13) Eloy, F. *J. Org. Chem.* **1961**, *26*, 952. Chang, M. S.; Matuszko, A. J. *Ibid.* **1963**, *28*, 2260. Reynolds, G. A.; Van Allan, J. A.; Tinker, J. F. *Ibid.* **1959**, *24*, 1205.

(14) Hoggarth, E. *J. Chem. Soc.* **1952**, 4811.

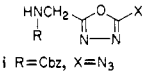
(15) If the reaction was not quenched with methyl iodide but worked up with aqueous acid instead, the intermediate 2-substituted 1,3,4-oxadiazoline-5-thiones i could be isolated.



i

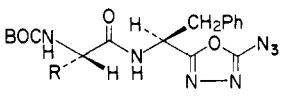
(16) Activation of the C-5 leaving group by oxidation to the sulfones **21** was necessary since the corresponding sulfides **20** were inert to azide even under forcing conditions.

(17) Attempted removal of the N-Cbz protecting group in compound i with HBr/acetic acid simultaneously converted the azide to the undesired amino functionality present in ii.

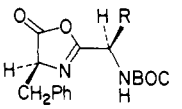


i R=Cbz, X=N_3
ii R=H, X=$NH_2 \cdot 2HBr$

(18) Fischer, E.; Mechel, L. *Chem. Ber.* **1916**, *49*, 1361.



24 R=CH_2Ph
25 R=H



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yield. Although no significant racemization was detected in the above transformations, further elaboration of substrates analogous to **24** and **25** did proceed with at least partial racemization, proceeding through a labile azalactone intermediate **26** in some cases.[19]

In summary, these results demonstrate that the concepts outlined in Scheme I are indeed feasible and can be reduced to practice. Table I catalogs the variety of substrates that undergo this synthetic sequence, proceeding in high overall yields. It is also quite clear that further development of our methodology is required. The combined effects of wavelength, solvent, sensitizers, and substrate upon the yield and optical integrity of the developing peptides are presently not fully investigated and require systematic study and evaluation. Additional applications of the peptidal azidooxadiazoles related to **5** as photoaffinity labels for important protease enzymes should be achieveable. Lastly, it is left to the imagination of the organic chemist to design and synthesize other heterocycles[20] that meet the rigid requirements of Scheme I and offer still other approaches to the classic challenge of peptide synthesis.

Experimental Section

Melting points were determined by the employment of a Kofler melting point block and were recorded uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137 and calibrated with 6.24-μm band of polystyrene. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer, using tetramethylsilane as an internal standard. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Mass Spectra were measured on a AEI Model MS-9 spectrometer utilizing a 70-eV ionizing potential. Elemental analyses were performed by the Scandanavian Microanalytical Laboratories, Herlev, Denmark. Preparative thick-layer chromatography plates were prepared with silica gel $PF_{254+366}$ and were 1.25 mm thick. After development, the sample was leached from the absorbent by extraction with 5% methanol in methylene chloride. Photolyses were carried out in a Srinivasan-Griffin Rayonet photochemical reactor or by exposure of the photolysate to an Hanovia 450-W low-pressure mercury lamp. All solvents and reagents were of commercial reagent grade and were used directly unless otherwise specified. Petroleum ether refers to low-boiling petroleum distillate (bp 39–54 °C).

5-(Acetoxymercuri)-1-(benzalamino)tetrazole (11). A solution of 101.4 g (0.289 mol) of mercuric acetate in 400 mL of water at 60 °C which was acidified by the addition of 10 mL of acetic acid was added in one portion to 50.0 g (0.289 mol) of 1-(benzalamino)tetrazole (**10**) in 700 mL of boiling 95% ethanol. The organomercury derivative began to separate within 1 min. The solution was allowed to cool to 25 °C, and 142.83 g (99%) of analytically pure product **11**, which separated as white needles, was collected by filtration and washed with warm benzene. The product, mp 110–111 °C, was insoluble in organic solvents and decomposed at temperatures above 120 °C: IR (KBr) 1580, 1300, 760, 690 cm^{-1}. Anal. Calcd for $C_{10}H_9N_5O_2Hg$ (431.80): C, 27.81; H, 2.10; N, 16.23. Found: C, 27.99; H, 2.40; N, 16.11.

5-Chloro-1-(benzalamino)tetrazole (12). With vigorous stirring gaseous chlorine was bubbled into 2 L of reagent acetone in which 428.51 g (0.97 mol) of 5-(acetoxymercuri)-1-(benzalamino)tetrazole (**11**) was suspended. After 36 min the last trace of the organomercury derivative disappeared, leaving a clear solution. The chlorine stream was immediately withdrawn, and the reaction mixture was cooled to 0 °C. A large crop of the desired chloro compound **12** crystallized as white needles, mp 140–144 °C, after 1 h. Additional material was obtained by evaporation of the filtrate under reduced pressure and recrystallization of the residue from $EtOH/H_2O$. The overall yield of pure **12** was 154.70 g (76%). For analysis a sample was recrystallized 6 times (EtOH) to yield hard white needles: mp 145.5–146.0 °C (after drying 24 h/60 °C in vacuo); IR (KBr) 1590, 1340, 1090, 975, 760, 690 cm^{-1}; NMR ($CDCl_3$) δ 7.3–8.1 (m, 5 H), 9.20 (s, 1 H); mass spectrum, *m/e* 207/209 (M^+), 144, 118, 103, 90 (base); UV (CH_3OH) max 216 (ϵ 9650), 285 (ϵ 20 500). Anal. Calcd for $C_8H_6N_5Cl$ (207.60): C, 46.30; H, 2.91; N, 33.74. Found: C, 46.33; H, 3.00; N, 33.53.

1-(Benzalamino)tetrazolone (13). To a solution of 10.00 g (48.2 mmol) of 5-chloro-1-(benzalamino)tetrazole (**12**) in 150 mL of 95% ethanol was added 100 mL of 1 N sodium hydroxide (corresponding to 100.0 mmol). The saponification was allowed to proceed for 2.0 h at the reflux temperature. The solution was cooled, acidified with 55 mL of 1 N hydrochloric acid (corresponding to 55 mmol), and evaporated under reduced pressure to afford a tan solid residue, which was extracted with two 40-mL portions of boiling benzene. The extracts were combined, diluted at 50 °C with petroleum ether, and the desired tetrazolone **13** separated as 7.47 g (82%) of white needles, mp 178–182 °C. For analysis a sample was recrystallized 4 times (benzene/petroleum ether) to yield hard white cubes: mp 182.2–182.4 °C (subliming above 160 °C); IR (KBr) 1695 (tetrazolone CO), 1055 (cyclic N—N=N), 955, 690 cm^{-1}; NMR (CD_3COCD_3) δ 2.6–4.4 (b, 1 H), 7.2–8.2 (m, 5 H), 9.2 (s, 1 H); mass spectrum, *m/e* 189 (M^+), 146, 118, 104, 103, 90 (base); UV (CH_3OH) max 215 nm (ϵ 9660), 266 (sh), 301 (ϵ 12 500). Anal. Calcd for $C_8H_7N_5O$ (189.20): C, 50.79; H, 3.73; N, 37.02. Found: C, 51.03; H, 3.75; N, 36.89.

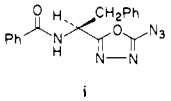
1-Aminotetrazolone (14). To 6.50 g (34.4 mmol) of 1-(benzalamino)tetrazolone (**13**) in 30 mL of water was added 15 mL of concentrated hydrochloric acid. A steam line was introduced and the benzaldehyde byproduct removed by steam distillation. The process was terminated after 45 min, and the clear solution was extracted with a 50-mL portion of benzene. The orange aqueous layer was evaporated under reduced pressure to leave an orange solid residue. The product was obtained pure by extracting the residue with warm 95% ethanol, which deposited the desired 1-aminotetrazolone (**14**) as 2.40 g (70%) of pale yellow cubes, mp 214–216 °C. For analysis a sample was washed 3 times with boiling benzene and twice with hot 95% EtOH, affording hard white cubes: mp 218.0–218.2 °C (subliming above 165 °C to diamond platelets); IR (KBr) 3410–3290 (NH_2), 1710 (CO), 1060 cm^{-1}; NMR (CD_3COCD_3) δ 4.0–7.0 (b, 3 H); mass spectrum, *m/e* 101 (M^+), 58 (base), 44, 43; UV (CH_3OH) max 220 nm (ϵ 2050). Anal. Calcd for CH_3N_5O (101.10): C, 11.88; H, 2.99; N, 69.29. Found: C, 12.00, H, 3.13; N, 69.76.

1-(Acetylamino)tetrazolone (15). A solution of 202 mg (2.0 mmol) of 1-aminotetrazolone (**14**), dissolved in 5 mL of acetic anhydride, was treated with 2 drops of trifluoroacetic acid and refluxed for 1.0 h. After cooling, the solution was mixed with 15 mL of methanol and evaporated under reduced pressure. The process was repeated 3 times. The tacky residue was dried 24 h/25 °C in vacuo and 2 weeks/25 °C in air to yield 236 mg (83%) of the desired acetyl derivative (**15**), mp 130–135 °C. For analysis a sample was recrystallized 6 times (acetonitrile/methylene chloride, 1:3) to yield small feathers: mp 136.0–137.0 °C; IR (KBr) 3280 (N-H), 1750 (tetrazolone), 1690 (amide CO), 1515 (secondary amide), 1255, 1050, 720 cm^{-1}. Anal. Calcd for $C_3H_5N_5O_2$ (143.10): C, 25.18; H, 3.52; N, 48.94. Found: C, 25.18; H, 3.57; N, 49.03.

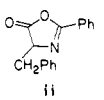
General Methodology for the Synthesis of 2-Substituted 5-(Methylthio)-1,3,4-oxadiazoles (20). A solution of 0.01 mol of an N-protected amino acid hydrazide **17** in 50 mL of ethanol at 25 °C is added 0.01 mol of potassium hydroxide followed by 0.011 mol of carbon disulfide. The reaction is heated under reflux until evolution of hydrogen sulfide ceases (4–22 h), cooled to room temperature, and treated with 0.011 mol of methyl iodide. The reaction is heated to reflux for 5 min, diluted with water, and cooled. The products **20** are isolated by filtration or extraction with methylene chloride (see Table I). Some specific examples follow.

2-[1-(*S*)-(*tert*-Butoxycarbonylamino)phenethyl]-5-(methylthio)-1,3,4-oxadiazole (29). To 5 mL of 95% ethanol were added 279 mg (1.0 mmol) of Boc·L·Phe·$NHNH_2$, mp 128–130 °C, 66 mg of potassium hydroxide (1.0 mmol), and 0.061 mL of carbon disulfide (1.1 mmol). The yellow solution was refluxed 4.0 h, cooled to 25 °C, treated with 0.062 mL of methyl iodide, heated to reflux, and after 5 min diluted with 5 mL of water, at which point the product **29** began to crystallize. The mixture was cooled and further diluted with an additional 15 mL of water, and after 20 min the fluffy white solid was collected and dried overnight in vacuo to yield 314 mg (95%) of the desired sulfide **29**, mp

(19) Evidence for an azlactone intermediate in the photolysis of the *N*-benzoyl derivative i was obtained by actually isolating 2-phenyl-4-benzyl-oxazolin-5-one ii, mp 87–88 °C (CH_3CN/hexane), identical with a sample prepared independently by DCC cyclodehydration of *N*-benzoylphenylalanine. See also: Goodman, M.; Levin, L. *J. Am. Chem. Soc.* **1964**, *86*, 2918.



i



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(20) A possible alternative may be based on the thermal fragmentation of 3-azido-1,2,4-oxadiazoles reported recently by Choi et al. (Choi, P.; Rees, C. W.; Smith, E. H. *Tetrahedron Lett.* **1982**, *23*, 121.

125–127 °C, as short cream needles. For analysis a sample was crystallized 3 times (ethanol/water) to yield long white needles: mp 126–127 °C; IR (KBr) 3390, (NH), 1680 (BOC), 1520 (secondary amide), 1150, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (s, 9 H), 2.7 (s, 3 H), 3.2 (d, J = 6 Hz, 2 H), 5.1–5.5 (b, 1 H), 5.3 (m, 1 H), 7.3 (s, 5 H); UV (CH_3OH) max 236 nm (ϵ 7180) (sh); $[\alpha]^{20}_D$ −34.6° (c 0.712, acetone). Anal. Calcd for $C_6H_{21}N_3O_3S$ (335.20): C, 57.30; H, 6.31; N, 12.53; S, 9.54. Found: C, 57.40; H, 6.40; N, 12.44; S, 9.73.

2-[1-(*S*)-(*tert*-Butoxycarbonylglycylamino)phenethyl]-5-(methylthio)-1,3,4-oxadiazole (31). To 15 mL of 95% ethanol was added 1.262 g (3.77 mmol) of BOC·Gly·Phe·$NHNH_2$, 0.248 g (3.77 mmol) of potassium hydroxide, and 0.251 mL (4.14 mmol) of carbon disulfide. The solution was refluxed 22.0 h, cooled to room temperature, and treated with 0.269 mL (4.14 mmol) of methyl iodide. The solution was heated on a steam bath 5 min and evaporated in vacuo, and the oily semisolid residue was dissolved in 100 mL of methylene chloride/water, 1:1. The organic layer was dried over sodium sulfate and evaporated under reduced pressure to yield 1.383 g (96%) of the expected product **31** as a light brown crystalline mass. The crude product was dissolved in hot 95% ethanol. Upon dilution with water, 1.062 g (74%) of pure sulfide **31** separated as a white microcrystalline power, mp 95–100 °C. For analysis a sample was recrystallized 4 times (ethanol/water; utilization of seeds is essential) to yield small, white prisms: mp 100–102 °C; IR (KBr) 3440, 3290 (NH), 1680 (BOC), 1660 (amide), 1510 (secondary amide), 1150 cm^{-1}; $[\alpha]^{25}_D$ −32.0° (c 0.750, acetone). Anal. Calcd for $C_{18}H_{24}N_4O_4S$ (392.40): C, 55.09; H, 6.17; N, 14.28; S, 8.15. found: C, 55.03; H, 6.14; N, 14.31; S, 8.21.

2-(*p*-Nitrophenyl)-5-(methylthio)-1,3,4-oxadiazole (27). A solution of 25.0 g (0.138 mol) of *p*-nitrobenzhydrazide in 200 mL of 95% ethanol was treated with 9.12 g (0.148 mol) of potassium hydroxide. The initially light yellow solution immediately became blood red. The reaction mixture was then treated with 8.35 mL (0.150 mol) of carbon disulfide and instantly changed to a deep purple color. The solution was refluxed 20.0 h as the color slowly turned orange-red. When the solution was cooled to 30 °C, a dark red crystalline mass separated (the potassium salt of *p*-nitrophenyl-Δ^2-1,3,4-oxadiazoline-5-thione). The salt was alkylated by the introduction of 9.35 mL (0.150 mol) of methyl iodide at 25 °C, and the bright red hue of the alkaline salt was discharged over the course of 5 min while the yellow microcrystalline product separated. After the mixture was cooled at 0 °C for 15 min, 26.90 g (83%) of the desired sulfide **27**, 152–156 °C, was collected by filtration. For analysis a sample was recrystallized 3 times from ethanol to yield yellow flakes: mp 158–160 °C; IR (KBr) 1560, 1340, ($ArNO_2$), 1190, 860, 850, 700, cm^{-1}. Anal. Calcd for $C_9H_7N_3O_3S$ (237.17): C, 45.57; H, 2.98; N, 17.22; S, 13.49. Found: C, 45.51; H, 2.93; N, 17.90; S, 13.54.

General Methodology for the Synthesis of 2-Substituted 5-(Methanesulfonyl)-1,3,4-oxadiazoles (21). A solution of 0.01 mol of the sulfide **20** in 20 mL of glacial acetic acid was treated dropwise at 25 °C with 0.021 mol of potassium permanganate as a 5% aqueous solution over 0.5 h. The reaction was allowed to proceed for an additional 1.5 h, decolorized by bubbling gaseous sulfur dioxide into the mixture, and diluted with 100 mL of water. The product was filtered and recrystallized (see Table I). Some specific examples follow.

2-[(Carbobenzyloxyamino)methyl]-5-(methanesulfonyl)-1,3,4-oxadiazole (35). A solution of 6.90 g (24.80 mmol) of the sulfide precursor of **36** in 60 mL of glacial acetic acid was treated dropwise with 8.60 g (55.0 mmol) of potassium permanganate in 170 mL of water over the course of 0.5 h. After an additional 1.5 h at 25 °C, the reaction mixture was treated with sulfur dioxide until colorless and diluted with 150 mL of water. The white solid sulfone that separated was collected and after drying represented 7.60 g (97%) of pure product **35**, mp 105–106 °C. For analysis a sample was recrystallized 3 times (ethanol) to yield white needles, mp 105.2–106.2 °C: IR (KBr) 3460 (NH), 1715 (CO), 1330, 1140 (SO_2), 690 cm^{-1}; NMR ($CDCl_3/Me_2SO$) δ 3.5 (s, 3 H), 4.6 (d, J = 6.0 Hz, 2 H), 5.1 (s, 2 H), 7.3 (s, 5 H), 7.5–7.8 (b, 1 H); UV (CH_3OH) max 274 nm (sh) (ϵ 3400). Anal. Calcd for $C_{12}H_{13}N_3O_5S$ (311.30): C, 46.31; H, 4.21; N, 13.50; S, 10.28. Found: C, 46.29; H, 4.29; N, 13.46; S, 10.33.

2-[1-(*S*)-(*tert*-Butoxycarbonylglycylamino)phenethyl]-5-(methanesulfonyl)-1,3,4-oxadiazole (36). A solution of 13.65 g (86.40 mmol) of potassium permanganate in 350 mL of water was added dropwise over 0.5 h to 16.10 g (41.20 mmol) of sulfide **32** in 150 mL of glacial acetic acid. After an additional 2.0 h at 25 °C, the reaction mixture was decolorized with sulfur dioxide, diluted with 400 mL of water, and extracted with three 100-mL portions of methylene chloride. The organic extracts were pooled and washed exhaustively with 10% sodium bicarbonate (foaming!) and water. After drying over sodium sulfate, the solution was evaporated under reduced pressure to give 17.38 g (100%) of the desired sulfone **36** as a colorless oil, which solidified to a white solid overnight. The crude product was recrystallized from ethanol/water (seeds must be used) and 15.90 g (93%) of pure product **36** was obtained. For analysis a sample was recrystallized 5 times (ethanol/water) to yield white fluffy needles: mp 123.3–125.9 °C; IR (KBr) 335 (NH), 1715 (BOC CO), 1690 (amide CO), 1340, 1145 (SO_2), 700 cm^{-1};$[\alpha]^{25}_D$ −26.6° (c 0.980, acetone). Anal. Calcd for $C_{18}H_{24}N_4O_6S$ (424.40): C, 50.94; H, 5.70; N, 13.20; S, 7.63. Found: C, 50.83, H, 5.76; N, 12.99; S, 7.63.

2-(*p*-Methoxyphenyl)-5-(methanesulfonyl)-1,3,4-oxadiazole (39). A solution of 19.00 g (0.120 mol) of potassium permanganate in 400 mL of water was added dropwise over 40 min to 12.70 g (0.0572 mol) of the sulfide precursor to **39** dissolved in 100 mL of glacial acetic acid. After stirring 1.5 h at 25 °C, the reaction mixture was decolorized with sulfur dioxide and diluted with 400 mL of water. The desired sulfone **39** separated as a white crystalline solid which was collected and dried to afford 13.60 g (95%) of crude product, mp 160–163 °C. For analysis a sample was recrystallized 4 times (ethanol) with large quantities of solvent to yield white translucent flakes: mp 164.8–166.4 °C; IR (KBr) 1610, 1445, 1330, 1145 (SO_2), 835 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_2O_4S$ (254.20): C, 47.25; H, 3.97; N, 11.02; S, 12.59. Found: C, 47.24; H, 3.61; N, 10.90; S, 12.57.

General Methodology for the Synthesis of 2-Substituted 5-Azido-1,3,4-oxadiazoles (22). A solution of 0.01 mol of the sulfone **21** in 30 mL of ethanol was treated with 0.02 mol of sodium azide in 6 mL of water. The solution was heated under reflux 10 min and diluted with 60 mL of water. When the mixture was cooled, the desired azide **22** separated and was isolated by filtration or extraction with methylene chloride (see Table I). Some specific examples follow.

2-[(Carbobenzyloxyamino)methyl]-5-azido-1,3,4-oxadiazole (50). A solution of 1.30 g (20.0 mmol) of sodium azide in 5 mL of water was added to 25 mL of 95% ethanol in which 2.97 g (10.0 mmol) of sulfone **37** had been dissolved. The resulting solution was refluxed 10 min and diluted with 10 mL of water. Immediately, the azide **50** began to crystallize and after 2.0 h was collected and air-dried to yield 2.13 g (82%) of **50** as translucent flakes, mp 108–109 °C. From the mother liquors a further crop of pure material was obtained, raising the overall yield to 2.48 g (96%). For analysis a sample was recrystallized 2 times (ethanol) to yield soft, white flakes: mp 108.6–109.1 °C; IR (KBr) 3410 (NH), 2190 (N_3), 1690 (Cbz CO), 1545, 690 cm^{-1}; NMR ($CDCl_3$) δ 4.5 (d, J = 6 Hz, 2 H), 5.1 (s, 2 H), 5.5–5.9 (b s, 1 H), 7.3 (s, 5 H); UV (CH_3OH) max 237 nm (ϵ 10 700). Anal. Calcd for $C_{11}H_{10}N_6O_3$ (274.20): C, 48.17; H, 3.68; N, 30.65. Found: C, 48.35: H, 3.83; N, 30.52.

2-[1-(*S*)-(*tert*-Butoxycarbonylamino)phenethyl]-5-azido-1,3,4-oxadiazole (45). A solution of 155 mg (2.38 mmol) sodium azide in 4 mL of water was added to 15 mL of 95% ethanol in which 436 mg (1.19 mmol) of sulfone **41** had been dissolved. After 10 min at reflux the solution was diluted with 20 mL of water and 354 mg (91%) of the desired azide **45** separated on cooling in the form of short needles, mp 115–118 °C. For analysis a sample was recrystalled 5 times (ethanol/water) to yield white needles: mp 115–117 °C; IR (KBr) 3390 (NH), 2190 (N_3), 1690 (Boc CO), 1590, 1540, 1160, 695 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (s, 9 H), 3.2 (d, 2 H), 5.2 (m, 1 H), 5.1–5.5 (b s, 1 H), 7.3 (m, 5 H); UV (CH_3OH) max 239 nm (ϵ 15 500), $[\alpha]^{20}_D$ = −26.1° (c 0.575, acetone). Anal. Calcd for $C_{15}H_{18}N_6O_3$ (326.30): C, 54.54; H, 5.49; N, 25.44. Found: C, 54.81; H, 5.65; N, 24.68.

2-(1-Naphthyl)-5-azido-1,3,4-oxadiazole (47). A solution of 2.60 g (40.0 mmol) of sodium azide in 150 mL of 95% ethanol/water (4:1), in which 5.48 g (20.0 mmol) of sulfone **38** had been dissolved, was refluxed 10 min. The hot solution was diluted with 50 mL of water and on cooling deposited 4.70 g (100%) of the desired azide **47** as pale yellow prisms, mp 83–84 °C. The product is light sensitive and must be immediately stored in an amber bottle. For analysis a sample was recrystallized in the dark 4 times (ethanol) to yield light yellow cubes: mp 84.4–87.7 °C; IR (KBr) 2160 (N_3), 1550, 1525, 1400, 770 cm^{-1}. Anal. Calcd for $C_{12}H_7N_5O$ (237.22): C, 60.75; H, 2.97; N, 29.53. Found: C, 60.97; H, 3.27; N, 29.62.

2-(Aminomethyl)-5-azido-1,3,4-oxadiazole (52). A sample of 483 mg (1.75 mmol) of the azide **46** in 5 mL of trifluoroacetic acid was stored at 25 °C for 0.25 h and diluted with 30 mL of anhydrous ether. The TFA salt of **52** separated and was collected and washed with ether to yield 398 mg (89%) of product, mp 128–129 °C. For analysis a sample was recrystallized 3 times from methanol/ether to yield white needles: mp 129–130 °C; IR (KBr) 3225–2940 (NH_3^+), 2190 (N_3), 1660 (CO_2^-), 1575, 1210, 1140, 835, 790, 720 cm^{-1}. Anal. Calcd for $C_5H_5N_6O_3F_3$ (254.14): C, 23.63; H, 1.98; N, 33.07. Found: C, 23.67; H, 2.18; N, 33.18.

The free base **52** was obtained as follows: A solution of 583 mg (2.26 mmol) of the above salt in 1 mL of water was added to 2.35 mL in sodium hydroxide in a separatory funnel. The mixture was extracted with 2 × 5 mL portions of methylene chloride. The organic layer was dried over magnesium sulfate and concentrated to 0.5 mL. The solution was

diluted with 2 mL of petroleum ether and stored in a freezer at −20 °C for 0.5 h. The desired free base **52** separated as 252 mg (80%) of small white flakes, mp 65–67 °C. For analysis a sample was recrystallized 5 times (methylene chloride/petroleum ether) to yield small translucent needles: mp 67–69 °C; IR (KBr) 3390, 3230 (NH_2), 2185 (N_3), 1605, 1410, 1220, 1040, 690 cm^{-1}; mass spectrum, *m/e* 140 (M^+), 70, 69, 56, 31, 30 (base); UV (CH_3OH) max 238 nm (ε 10 130). Anal. Calcd for $C_3H_4N_6O$ (140.10): C, 25.72; H, 2.88; N, 59.99. Found: C, 25.81; H, 3.35; N, 60.31.

2-(1-(*S*)-Aminophenethyl)-5-azido-1,3,4-oxadiazole (53). To 2 mL of anhydrous trifluoroacetic acid was added 326 mg (1.0 mmol) of the azide **45**. After 10 min at 25 °C the solution was diluted with 20 mL of anhydrous ether, forcing a crystalline salt to separate. The product was collected, washed thoroughly with excess ether, and dried to afford 243 mg (71%) of **53** as its TFA salt, white fluffy needles, mp 145–150 °C dec. For analysis a sample was recrystallized 4 times (methanol/ether, 1:6) to yield white needles, mp 145–150 °C dec; IR (KBr) 3570–3030 (NH_3^+), 2185 (N_3), 1675 (CO_2^-), 795, 710, 690 cm^{-1}.

The free base **53** was obtained as follows: To 4 mL of 1 N sodium hydroxide (4.0 mmol) was added 451 mg (1.31 mmol) of the above trifluoroacetate salt. The white oil which separated was immediately extracted into two 10-mL portions of methylene chloride. The organic phases were combined, dried over magnesium sulfate, and evaporated under reduced pressure to afford 303 mg (100%) of the desired azide **53** as a colorless oil. The product was taken up in a minimum amount of methylene chloride and diluted with petroleum ether until turbid. After addition of a drop of the former solvent to restore clarity, the solution was stored in a freezer at −20 °C, and crystalline flakes of **53** were deposited within 0.5 h. For analysis a sample was recrystallized 3 times (methylene chloride/petroleum ether) to yield colorless refractive needles: mp 71.0–71.9 °C; IR (KBr) 3400, 3370 (NH_2), 2185 (N_3), 1590, 1025, 700 cm^{-1}; mass spectrum, *m/e* 230 (M^+), 219, 144, 140, 139 (base), 91, 57. Anal. Calcd for $C_{10}H_{10}N_6O$ (230.23): C, 52.17; H, 4.38; N, 36.51. Found: C, 52.01; H, 4.46; N, 36.36.

Photolysis of 2-((Tosylamino)methyl)-5-azido-1,3,4-oxadiazole (43). A solution of 15.0 mg (0.05 mmol) of azide **43** in 8 mL of ethanol/benzene, 1:1, was irradiated for 3 h with 375-nm UV light in a Rayonet apparatus. The solution was evaporated to afford pure Ts-Gly-OEt, identical in all respects with an authentic sample,[18] in quantitative yield.

Photolysis of 2-Phenyl-5-azido-1,3,4-oxadiazole (6, R = Ph). A solution of 19 mg (0.01 mmol) of the azide **6** (R = Ph) in 5 mL of methylene chloride was irradiated 2 h under the above conditions. Evaporation afforded pure benzoyl cyanide in quantitative yield. The product was identical in all respects with an authentic sample.[18a]

Photolysis of 2-(1-Naphthyl)-5-azido-1,3,4-oxadiazole (47). A solution of 24 mg (0.1 mmol) of the azide **47** in 10 mL of methylene chloride was irradiated for 0.67 h with 375-nm UV light in a Rayonet. The solution was evaporated to yield 17 mg (94%) of pure 1-naphthoyl cyanide identical in all respects with an authentic sample.[6a] The product was taken up in 4 mL of methylene chloride and treated with 10.9 μL (0.1 mmol) benzylamine. After 1 h at 25 °C the solution was evaporated to yield 25 mg (99%) of pure 1-naphthoic acid benzamide, mp 121–122 °C. For analysis, a sample was recrystallized 3 times (EtOH) to yield white fluffy needles: mp 121–122 °C; IR (CH_2Cl_2) 2500 (NH), 1665 (amide CO), 1515 (secondary amide) cm^{-1}. Anal. Calcd for $C_{18}H_{15}NO$ (216.31): C, 82.73; H, 5.79; N, 5.36. Found: C, 82.60; H, 5.83; N, 5.39.

Photolysis of 2-*n*-Undecyl-5-azido-1,3,4-oxadiazole (48). As above, photolysis of the *n*-undecyl azide **48** and treatment with benzylamine yielded the benzamide of lauric acid, mp 80–83 °C, in 60% overall yield, identical with an authentic sample.[21]

(21) Bowen, C. V.; Smith, L. E. *J. Am. Chem. Soc.* **1940**, *62*, 3522.

Photolysis of 2-[1-(*S*)-(*tert*-Butoxycarbonylamino)phenethyl]-5-azido-1,3,4-oxadiazole (45). A solution of 300 mg (0.92 mmol) of azide **45** in 50 mL of dry methylene chloride was irradiated in a Rayonet with 375-nm UV light. After 4.5 h the solution was treated with 0.112 mL (1.02 mmol) of benzylamine. After 1 h at 25 °C the solution was extracted with 1 N hydrochloric acid, dried over sodium sulfate, and evaporated to yield 204 mg (65%) of pure BOC-Phe-$NHCH_2Ph$ which was recrystallized from ethanol/water to give white needles: mp 131–132 °C; IR (KBr) 3000 (NH), 1685 (Boc CO), 1660 (amide CO), 1520 (secondary amide), 1280, 1160, 690 cm^{-1}; $[\alpha]^{20}_D$ −12.1° (*c* 1.20, acetone). Anal. Calcd for $C_{21}H_{26}N_2O_3$ (354.43): C, 71.16; H, 7.39; N, 7.90. Found: C, 71.10; H, 7.30; N, 7.95.

In a similar fashion the above photolysate derived from 33 mg (1.0 mmol) of the azide **45** was treated with 23 mg (1 mmol) of the amino heterocycle **53** to yield 24 mg (53%) of the dipeptide derivative **24**: mp 121–124 °C; IR (KBr) 3370 (NH), 2180 (N_3), 1690 (Boc CO), 1670 (amide CO).

Preparation of Boc-L-Phe-$NHCH_2Ph$ by Curtius Procedure. A solution of 162 mg (0.57 mmol) Boc-L-Phe-$NHNH_2$ in 8 mL of 1 N hydrochloric acid was cooled to −10 °C by immersion in an ice/sodium chloride/sulfuric acid bath. In one portion 0.5 mL of water in which 44 mg (0.64 mmol) of sodium nitrite had been dissolved was added. The precipitated Boc-L-Phe-N_3, which separated as a white solid, was extracted into anhydrous ether at 0 °C, washed at that temperature with water, 10% sodium bicarbonate, and water again, dried over magnesium sulfate, and treated with 64 mg (0.66 mmol) of benzylamine. The solution was stirred for 8.0 h at 0 °C and stored overnight in a water bath. The solution was extracted with an equal volume of methylene chloride, and the organic phase was washed with 10% citric acid at 0 °C, 10% sodium bicarbonate, and finally water. After drying over magnesium sulfate, the solution was evaporated to give a colorless oily residue, which solidified readily on scratching to yield 181 mg (88%) of the expected benzamide as a white solid, mp 131–132 °C, identical with material produced by the preceding photolysis of the azide **45** and treatment with benzylamine.

Photolysis of 2-[1-(*S*)-(*tert*-Butoxycarbonylglycylamino)phenethyl]-5-azido-1,3,4-oxadiazole (25). A solution of 76 mg (0.2 mmol) of the azide **25** in 5 mL of methylene chloride was treated with 20 μL (0.2 mmol) of benzylamine and irradiated for 2.0 h with 375-nm UV light. The mixture was extracted with 1 N hydrochloric acid, dried and evaporated to yield 80 mg (97%) of Boc-Gly-Phe-$NHCH_2Ph$, mp 141–142 °C (EtOH), identical with an authentic sample prepared by the following procedure: A solution of 336 mg (1.0 mmol) of Boc-Gly-Phe-$NHNH_2$ in 15 mL of 1 N hydrochloric acid was cooled to −5 °C in an ice–salt bath. To this was added 76.0 mg (1.10 mmol) of sodium nitrite in 1 mL of ice water. After 3 min 30 mL of methylene chloride, previously cooled to 0 °C, was added. The organic phase was then washed at 0 °C with water, 10% sodium bicarbonate, and again with water. The solution was dried over sodium sulfate and treated with 0.122 mL of (1.1 mmol) benzylamine in 5 mL of methylene chloride. The mixture was stirred at 0 °C for 6.0 h and stored overnight in a water bath. After the addition of 30 mL of methylene chloride, an insoluble contaminant was filtered. The filtrate was washed with water, at 0 °C with 10% citric acid, 10% sodium bicarbonate, and water. After drying over sodium sulfate, the solution was evaporated under reduced pressure to yield 280 mg (68%) of the benzamide as a colorless foam, which was taken up in hot 95% ethanol. White needles, which melted at 140–141 °C, were deposited after the addition of water and cooling. For analysis a sample was recrystallized 3 times (ethanol/water) to yield white, refractive platelets, mp 141.5–142.0 °C; IR (KBr) 3355, 3185 (NH), 1695 (Boc CO), 1655, 1645, 1270, 1240 cm^{-1}; $[\alpha]^{25}_D$ −11.7° (*c* 1.08, DMF). Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.13; H, 7.10; N, 10.21. Found: C, 67.15; H, 7.18; N, 10.18.