

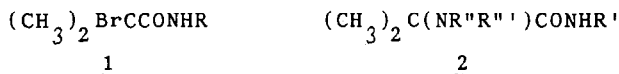
MODEL DEPSIPEPTIDE DERIVATIVES FROM  
 2-BROMO-N-BENZYLISOBUTYRAMIDE

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Summary: 2-Bromo-N-benzylisobutyramide reacts with N-protected aminoacids in the presence of silver oxide to afford the pertinent depsipeptide derivatives in mild conditions, high yields and short time.

2-Bromo-carboxamides 1 are useful starting material for a wide variety of derivatives. Base-induced reactions give rise to series of linear and cyclic polifunctionalized products<sup>1</sup> and permit the synthesis of sterically hindered 2-amino-carboxamides 2<sup>2</sup>. We wish now to report a facile and high-yield method for the formation of the ester linkage of model depsipeptides via the substitution of the bromine at the 2-carbon of the starting amide by the carboxyl group of a protected  $\alpha$ -aminoacid.



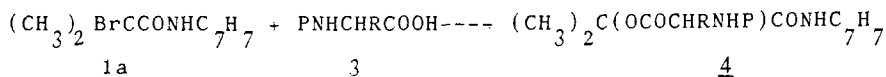
Synthesis of depsipeptides is encumbered with difficulties, and methods so far available suffer from several drawbacks, including poor yields, side reactions, prolonged reaction time<sup>3</sup>. In spite of novel methods of esterification of carboxylic acids recently proposed<sup>4</sup>, depsipeptide synthesis generally uses N,N-dicyclohexylcarbodiimide in the presence of 4-(N,N-dialkylamino)-pyridine as a catalyst.<sup>5</sup>

In this communication we describe a new approach to the formation of the ester linkage based on the direct coupling of N-protected aminoacids with a 2-bromo-isobutyramide in the presence of silver oxide.

2-Bromo-N-benzyl-isobutyramide 1a reacts with equimolecular amounts of a -protected aminoacid 3 and silver oxide<sup>6</sup> in a one-pot operation at room

temperature, to afford high yields of a pure ester-amide derivative 4 (Equation 1). No racemization has been observed by the routine tests.<sup>7</sup> Model products obtained are shown in the Table.

(Eq.1)



where P=Z or Boc.

All compounds showed correct C,H,N analysis. Tlc indicated only one product. I.R. spectra showed the appearance of the CO stretching absorption band of the ester linkage near  $1740 \text{ cm}^{-1}$ . The formation of the ester linkage can be followed through N.M.R.: the singlet at 1.98 ppm due to the  $(\text{CH}_3)_2\text{C}$  protons of the starting bromoamide, shifts near 1.50 ppm for compounds 4b, 4d, 4h splitting into two singlets in compounds 4a, 4c, 4e, 4f, 4g.

#### Typical procedure

To a solution of a N-Boc- or N-Z-aminoacid (0,001 mol) and 2-bromo-N-benzylisobutyramide (0,001 mol) in 5 ml of  $\text{CH}_3\text{CN}$ , silver oxide (0,001 mol) was added. The reaction mixture was stirred at room temperature and monitored by tlc on silica gel; visualisation by exposure to  $\text{J}_2$  vapor. The silver salts were eliminated by passing the solution on a column filled by neutral alumina (Merck) covered with a layer of Celite 577 (Fluka) and the filtrate was evaporated to dryness. The resulting crude products were purified using ethyl ether-light petroleum and dried in vacuo on  $\text{P}_2\text{O}_5$ .

Studies on the mechanism and scope of the present method are in progress.

(\*) Abbreviations: Z=benzyloxycarbonyl; Boc=tert-butyloxycarbonyl; Hib=2-hydroxyisobutyryl; Aib=2-amino-isobutyryl.

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Table of depsipeptide derivatives, obtained at room temperature using  $\text{Ag}_2\text{O}$  in  $\text{CH}_3\text{CN}$ .

Depsipeptide derivatives 4	React. time (h)	Yield (a) %	m.p. °C	$^1\text{H-NMR}$ (b)
(a) Z-Ala-Hib-NH-Bz	3	99	oil	1.36 (d, J=7.28 Hz, 3H), 1.58 (s, 3H), 1.61 (s, 3H), 4.16 (m, 1H), 4.41 (d, J=5.78 Hz, 2H), 4.87 (AB, J=12 Hz, 2H), 5.45 (d, J=5.94 Hz, 1H), 7.09 (br, 1H).
(b) Z-Alb-Hib-NH-Bz	3	94	105-6	1.46 (s, 6H), 1.50 (s, 6H), 4.42 (d, J=5.72 Hz, 2H) 4.85 (s, 2H), 5.16 (s, 1H), 7.23 (br, 1H)
(c) Z-Phe-Hib-NH-Bz	3	91	98-100	1.51 (s, 3H), 1.54 (s, 3H), 3.04 (d, J=7.26 Hz, 2H) 4.26-4.47 (m, 2H, 1H), 4.88 (AB, J=12.44 Hz, 2H), 5.20 (d, J=5.90 Hz, 1H), 6.68 (br, 1H).
(d) Boc-Met-Hib-NH-Bz	12	84	oil	1.33 (s, 9H), 1.64 (s, 6H), 1.97 (m, 2H), 2.06 (s, 3H), 2.55 (t, J=7.5 Hz, 2H), 4.43 (d, J=5.12 Hz, 2H, m, 1H), 5.34 (d, J=6.42 Hz, 1H)
(e) Boc-Trp-Hib-NH-Bz	5	88	oil	1.32 (s, 9H), 1.50 (s, 3H), 1.51 (s, 3H), 3.21 (d, J=6.9 Hz, 2H), 4.27 (d, J=5.74 Hz, 2H), 4.45 (m, 1H), 5.10 (d, J=5.66 Hz, 1H), 6.87 (br, 1H), 8.45 (s, 1H)
(f) Boc-Pro-Hib-NH-Bz	3	98	64-65	1.31 (s, 9H), 1.57 (s, 3H), 1.65 (s, 3H), 1.84-2.25 (2m, 2H+2H), 3.43 (m, 2H), 4.18 (x of ABX, J <sub>ax</sub> =8 Hz, J <sub>bx</sub> =6 Hz, 1H), 4.43 (AB of ABX, J <sub>ax</sub> =14.79 Hz, J <sub>bx</sub> =14.18 Hz, J <sub>ab</sub> =6 Hz, 2H), 7.68 (br, 1H)
(g) Boc-Cys(S-Bz)-Hib-NH-Bz	3	86	94-6	1.37 (s, 9H), 1.60 (s, 3H), 1.66 (s, 3H), 2.77 (d, J=5.9 Hz, 2H), 3.63 (s, 2H), 4.25 (x of ABX, J <sub>bx</sub> =5.9 Hz, J <sub>ax</sub> =12.2 Hz, 1H), 4.43 (d, J=5.7 Hz, 2H), 5.2 (br, 1H).
(h) Boc-Aib-Hib-NH-Bz	3	90	134-6	1.27 (s, 9H), 1.42 (s, 3H), 1.58 (s, 3H), 4.43 (d, J=5.82 Hz, 2H), 4.94 (s, 1H), 7.65 (br, 1H)

a) Yields are referred to pure products obtained from percolation on column of the reaction mixture, followed by concentration to dryness.

b) Spectra were determined with a Bruker AC 200 spectrometer at 200 MHz. Chemical shifts of deuteriochloroform solutions are expressed in  $\delta$  ppm downfield from the signal of tetramethylsilane used as internal standard. Chemical shifts of aromatic protons are omitted.

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