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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[1] and permit the synthesis of sterically hindered 2-amino-carboxamides 2[2]. 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 α-aminoacid.

$(CH_3)_2BrCCONHR$ (1) $(CH_3)_2C(NR"R"')CONHR'$ (2)

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

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[6] 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.[7] Model products obtained are shown in the Table.

(Eq.1)

$$(CH_3)_2BrCCONHC_7H_7 + PNHCHRCOOH \text{----} (CH_3)_2C(OCOCHRNHP)CONHC_7H_7$$

1a 3 4

where P=Z or Boc.

All compounds showed correct C,H,N analysis. Tlc indicated only one product. I.R. spectra showed the appearence of the CO stretching absorption band of the ester linkage near 1740 cm^{-1}. The formation of the ester linkage can be followed through N.M.R.: the singlet at 1.98 ppm due to the $(CH_3)_2C$ 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 CH_3CN, 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 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 P_2O_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 Ag_2O in CH_3CN.

	Depsipeptide derivatives 4	React. time (h)	Yield[a] %	m.p. °C	^{1}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=12Hz, 2H), 5.45 (d, J=5.94Hz, 1H), 7.09 (br, 1H).
(b)	Z-Aib-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=12.44Hz, 2H), 5.20.(d, J=5.90Hz, 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, Jax=8 Hz, Jbx=6 Hz,1H), 4.43 (AB of ABX, Jax=14.79Hz, Jbx=14.18Hz, Jab=6Hz, 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, Jbx=5.9 Hz, Jax=12.2 Hz, 1H), 4.43 (d, J=5.7Hz, 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 δ ppm downfield from the signal of tetramethylsilane used as internal standard. Chemical shifts of aromatic protons are omitted.

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7. Data to be published.

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