Preparation of Optically Pure Monoacyl 2-Alkyl *gem*-Diamines from Peptide Amides

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The treatment of peptide amides with [bis(trifluoroacetoxy)iodo]benzene yields monoacyl 2-alkyl *gem*-diamines of high optical purity as determined by reverse-phase h.p.l.c.

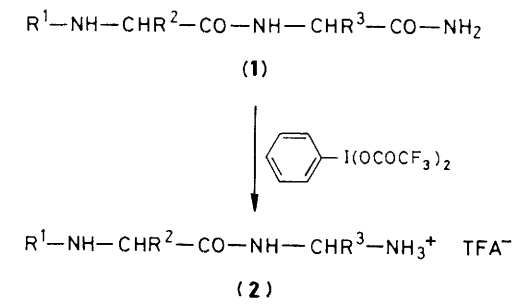
Optically active monoacyl 2-alkyl *gem*-diamines are of interest because they are useful intermediates in the syntheses of partial retro-inverso modified peptides.[1]† Alternative routes to these compounds include the Curtius, Hofmann, and Schmidt rearrangements. The Curtius route is laborious and requires an additional deprotection step to prepare the target molecule, whereas the Hofmann and Schmidt rearrangements are of limited applicability for peptides because of the harsh conditions used.[2]

Here we report the synthesis of optically pure monoacyl 2-alkyl *gem*-diamines (**2**) directly from their peptide amide precursors (**1**) using [bis(trifluoroacetoxy)iodo]benzene (TIB) first used by Loudon as an amide-to-amine conversion reagent to prepare nonchiral alkyl amines,[3]‡ and for *C*-terminal sequential degradation.[4] We have employed TIB for the conversion of peptide amides into optically pure monoacyl *gem*-diamines in good to excellent yields. In a typical procedure a urethane-protected dipeptide is dissolved or suspended in *ca.* 50% aqueous acetonitrile and treated with 1—1.05 equiv. of TIB for 3 h at room temp. Upon completion of the reaction, which is conveniently followed by t.l.c., the product is dried by lyophilization or over P_2O_5 after repeated evaporation with acetonitrile. Filtration from di-isopropyl ether or diethyl ether provides a pure material in good yield. Representative syntheses are shown in Table 1.

Table 1. Characterization[a] of 2-alkyl *gem*-diamines (**2**).

gem-Diamine trifluoroacetate	Yield[b]/%	M.p./°C	$[\alpha]_D$[c]
Fmoc-Ala-*g*-Phe	80	146—147	+5.3[d]
Boc-Phe-*g*-Phe	87	132—135	−37.2
Boc-Phe-*g*-D-DPhe	92	143—144	+33.9
Boc-Phe-*g*-Ala	93	142—143	−16.8
Boc-Gly-*g*-Phe	75	126—128	−9.9
Boc-Gly-*g*-D-Phe	82	114—115	9.86

[a] The products were also characterized by ^{1}H n.m.r. spectroscopy, h.p.l.c., and t.l.c. [b] Yields are given for the purified products and are not optimized. [c] *c* 1, MeOH. [d] In *N*,*N*-dimethylformamide.



† An isomer of a linear peptide in which the direction of the sequence is reversed and the chirality of each amino-acid residue is inverted is termed a retro-inverso isomer.

‡ In a very recent application TIB has been used for the conversion of the β-carboxamide of protected asparagine into the diaminopropionic acid derivative: M. Waki, Y. Kitajima, and N. Izumiya, *Synthesis*, 1981, 266.

Since this is the first preparative application of the reagent for peptides, we were concerned about the possibility of racemization at the chiral centre adjacent to the amine which is formed in the reaction. Even though the reaction takes place *via* the isocyanate[3] and therefore should occur with retention of configuration,[5] some racemization under the conditions used cannot be excluded *a priori*. To examine racemization, diastereomers of selected dipeptide amides were synthesized and subjected to treatment with TIB. The separation of diastereomers of the *gem*-diamines was accomplished by reverse-phase h.p.l.c. The best separation was achieved for

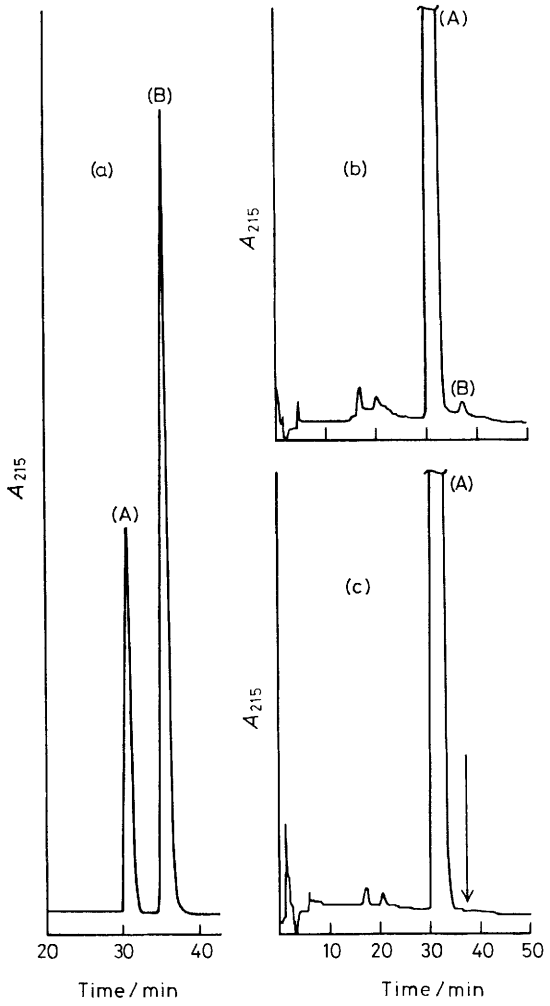


Figure 1. H.p.l.c. separation of diastereomers of Boc-Phe-*g*-Phe. (a) Separation of Boc-Phe-*g*-Phe (A) and Boc-Phe-*g*-D-Phe (B) mixed in ratio 1:2; (b) 99.7% Boc-Phe-*g*-Phe (A) +0.3% Boc-Phe-*g*-D-Phe (B), 200 μg sample injection; (c) 200 μg Boc-Phe-*g*-Phe, arrow indicates the retention time of Boc-Phe-*g*-D-Phe. Note the absence of the latter. Conditions: analytical Lichrosorb RP-18 column, linear gradient 38 → 45 II 40 min, solvents I: 0.25 N triethylammoniumphosphate, pH 2.25, II: 40% I in MeCN, 2 ml/min.

Boc-Phe-*g*-Phe§ and Boc-Phe-*g*-D-Phe [shown in Figure 1(a)]. That both products gave rise to only one isomer was manifested by the appearance of only one peak in the h.p.l.c. separation. Contamination by the other diastereomer of 0.3% (artificially mixed) could be clearly detected [Figure 1(b)]. Thus, racemization accompanying conversion with **TIB** is substantially less than this amount. The trifluoroacetates of the monoacyl *gem*-diamino-peptide derivatives are stable as solids for at least several months and they are reasonably stable under normal peptide synthetic manipulations. This is in agreement with Loudon's observation[6] that this type of compound, though decomposing under hydrolytic conditions, has higher stability than would be expected from its masked aldehyde structure.

The general applicability of the TIB method to peptides is apparent from the above findings. For preparative purposes, peptide amides are convenient precursors and the amide provides an excellent protecting group. Compatibility is anticipated between the above-described TIB treatment and a wide variety of protecting groups with some known exceptions.[7] Since **TIB** is a mild oxidative reagent, oxidation-sensitive amino-acids may undergo side reactions.[8]

§ *g* = *gem*, refers to the 2-alkyl *gem*-diamino-derivative of the corresponding amino-acid.

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