Benzotriazole-assisted Synthesis of Monoacyl α-Aminoglycines

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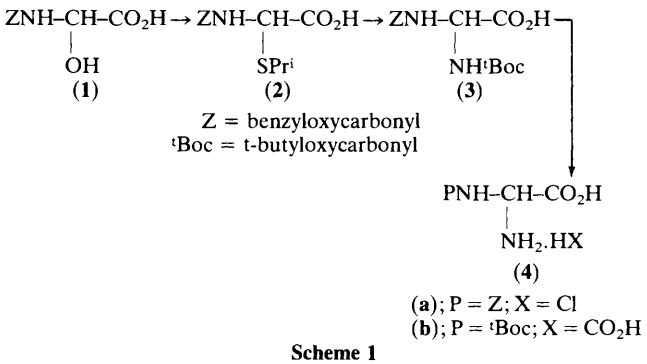
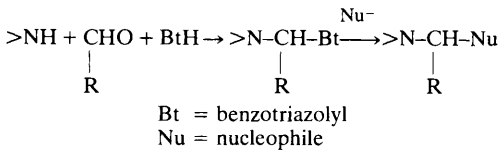
Adducts (**8,12**), derived from benzotriazole (**7**), glyoxylic ester (**6**) or acid (**11**), and an amide (**5**), react with ammonia in a novel, convenient route to monoacylated α-aminoglycines (**9,13**) useful for the synthesis of peptide analogues.

Reversing one or more of the amide groups (*i.e.* –CHRCONH– to –CHRNHCO–) of a linear peptide gives a so called 'partially modified retro isomer' and represents an important strategy in peptide analogue research.[1a,2] The modified sequence requires both a malonic unit and an (much less easily available) α,α-diamino moiety. Such α,α-diamino units have been synthesized by Curtius-[1,3,5] or Hoffmann-type[2,3,4] rearrangement of appropriately protected amino acid derivatives. Recently, Bock and co-workers[6] obtained protected α-aminoglycines (**4**) from α-hydroxy-*N*-(benzyloxycarbonyl)glycine (**1**) *via* intermediates (**2**) and (**3**) (Scheme 1); direct reaction of (**2**) with NH_3 did not give (**4**).

Earlier we reported[7] convenient syntheses of compounds of type >N–CHR–X mediated by benzotriazole by the general route of Scheme 2. More recently, this methodology with ethyl glyoxylate as oxo-component (R = CO_2Et) and organozinc



Scheme 1



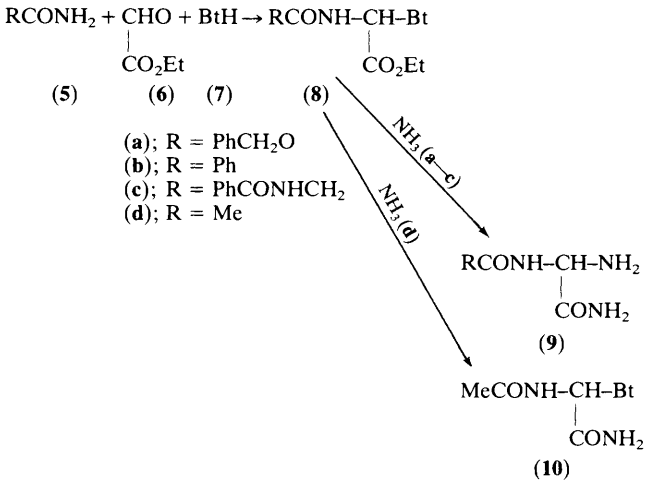
Scheme 2

carbanion nucleophiles (Nu = alkyl, aryl) allowed the synthesis of α-dialkylaminoesters.[8] Extension of this work to *N*-nucleophiles has now led to the first direct synthesis of monoacyl-α-aminoglycines.

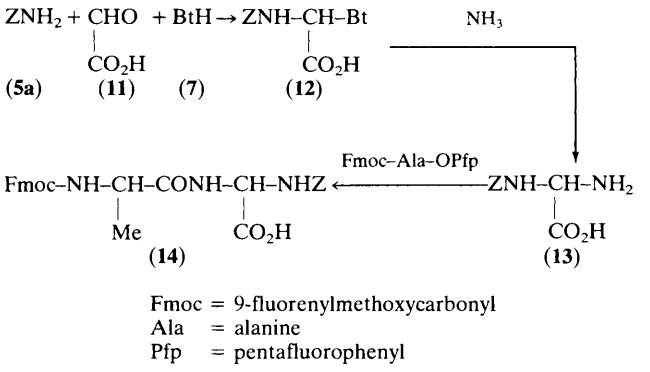
Condensations of various amides (**5a**—**d**), benzotriazole (**7**) and ethyl glyoxylate (**6**) (in toluene and *p*-toluenesulphonic acid catalyst) under Dean–Stark conditions gave adducts (**8a**—**d**) in 70—75% yield (Scheme 3). Amide (**5a**), benzotriazole and glyoxylic acid (**11**) (in benzene) similarly gave (**12**) (78%, Scheme 4). Reactions of electrophilic acylglycine synthons (**8b,c**) and (**12**) with methanolic NH_3 afforded the α-amino-*N*-acylglycines (**9b,c**) and (**13**) in good yields (86, 98 and 70% respectively), simultaneous amidation of the ester function having occurred. Similar reaction of (**8a**) afforded (**9a**) together with dimer product; in aqueous ammonia (**9a**) was isolated in 37% yield. The work-up procedure is easy: simple filtration in the aqueous case, or evaporation of the methanol and isolation with an appropriate solvent [acetone for (**13**), ether for the others], afforded solid products in a practically pure state. The side-product benzotriazole was removed in the mother liquor. The reactivity of the α-carbon centre depends on the character of the acyl group (RCO): in the case of R = Me (**8d**), overnight reaction with methanolic NH_3 at 5 °C led almost selectively to amide (**10**). However, some formation of benzotriazole was observed (TLC) in these reactions as well, indicating that the replacement of the Bt-moiety should be attainable under the appropriate conditions. Compounds (**9a**—**c**) and (**13**) are stable at room temperature, however, attempted recrystallization of (**9a**) from boiling EtOH led to quantitative dimerization to $[ZNHCH(CONH_2)]_2NH$.

Application of the synthesized α-amino-*N*-acylglycines for peptide synthesis was tested by reaction of amino acid (**13**) with fluorenylmethoxycarbonylalanine pentafluorophenyl ester (Fmoc–Ala–OPFP) under the usual conditions[9] to yield the expected dipeptide Fmoc–Ala–Gly(NHZ)–OH (**14**). However, the preparation of such peptides possessing the α-aminoglycine unit in the C-terminal position is more conveniently effected directly by our benzotriazole-assisted 'glycination' method as illustrated by the synthesis of dipeptide (**9c**).†

† All new compounds were fully characterized by C,H,N analyses and by ^{13}C- and ^{1}H-n.m.r. spectra.



Scheme 3



Scheme 4

Preliminary results indicate that this method can be applied to primary and secondary amines as nucleophiles, as well as to simple aliphatic and aromatic aldehydes as oxo-components. These extensions should provide a general route to monoacyl-α,α-diamino compounds.

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