A Base-labile Amine Component in Four-component Condensation (4CC) Synthesis

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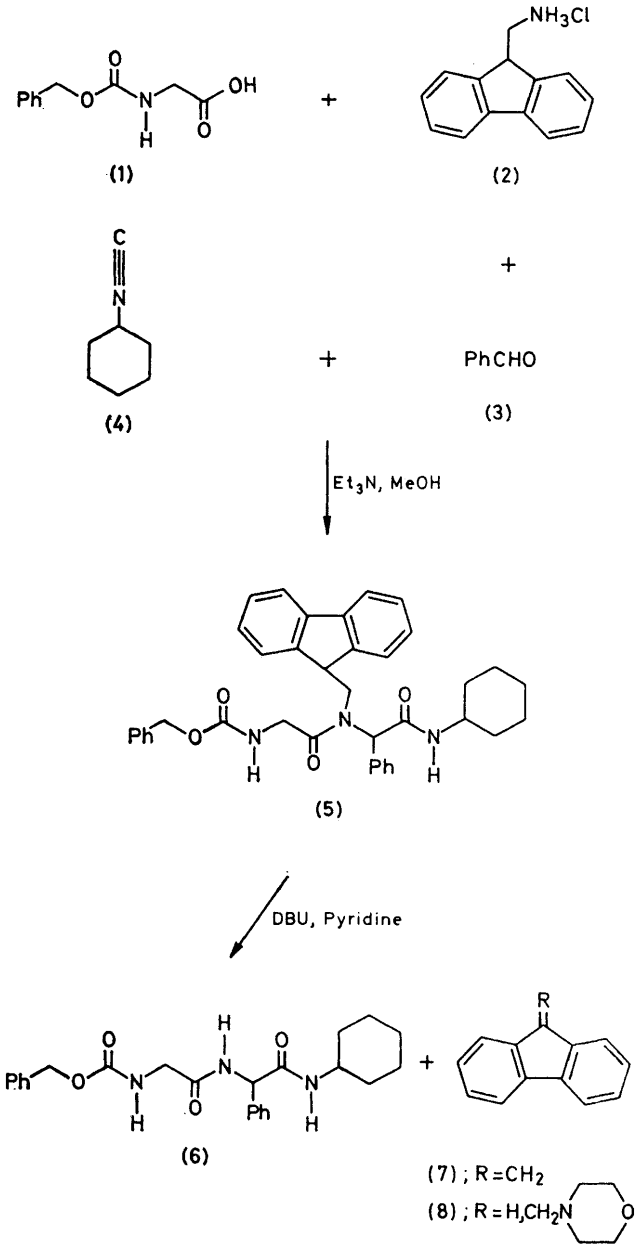
Summary The use of 9-aminomethylfluorene as the amine component in four-component condensation (4CC) synthesis is described for a model peptide synthesis.

THE advantage in utilizing 9-formylfluorene as the aldehyde component in four-component condensation fragment-strategy peptide synthesis (4CC fragment condensation) has been demonstrated.[1] The base lability of 9-(heteroatom methyl)-substituted fluorenes[2] offers the use of 9-aminomethylfluorene as the amine component in the one-step construction of tripeptide derivatives (4CC synthesis).[3,4] We report herein our results in the application of this amine to 4CC synthesis of a model dipeptide.

9-Aminomethylfluorene (**2**) was prepared in several steps from fluorene-9-carboxylic acid. The commercially available acid by reaction in neat oxalyl chloride provided fluorene-9-carbonyl chloride.[5] The acid chloride was dissolved in dioxan and treated with anhydrous ammonia to yield 9-fluorenecarboxamide.[5] Reduction of the amide was accomplished with 10 equiv. of sodium trifluoroacetoxyborohydride[6] in dioxan at 60 °C for 5 h. The amine product[7] was isolated and spectroscopically characterized as the hydrochloride salt. 9-Aminomethylfluorene hydrochloride (**2**), m.p. 261—265 °C (decomp.); ^{1}H n.m.r. (CD_3SOCD_3–D_2O) δ 3·30 (2 H, d, *J* 6 Hz, CH_2), 4·27 (1 H, t, *J* 6 Hz, CH), and 7·17—7·86 (8 H, m, aryl), was obtained from fluorene-9-carboxylic acid in 33% overall yield.

Reaction of 0·40 mmol of (**2**) with equimolar quantities of *N*-benzyloxycarbonylglycine (**1**), benzaldehyde (**3**), and cyclohexyl isocyanide (**4**) was performed in 3·0 ml of methanol containing 1 equiv. of triethylamine at room temperature for a period of 16 h. Work-up as previously described[1] yielded compound (**5**),† recrystallized from diethyl ether (76%), m.p. 154—155 °C; δ($CDCl_3$) 0·91—2·10 (11 H, m alkyl CH), 3·14—3·81 (5 H, m, NCH_2CO and NCH_2CH), 4·93 (2 H, s, CH_2OCO), 5·78 (1 H, br.s, CH), and 6·98—7·67 (18 H, m, aryl CH). The condensation product was homogeneous as indicated by t.l.c. on Merck $60F_{254}$ silica gel with 1% methanol in chloroform (R_F 0·38) or ethyl acetate (R_F 0·75) as eluant.

Removal of the *N*-fluoren-9-ylmethyl substituent was accomplished in excellent yield by reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Treatment of 0·125 mmol of (**5**) with 1·1 equiv. of DBU in 0·35 ml of pyridine at room temperature effected removal of the substituent group in 6 h. Reaction progress was followed by t.l.c. The reaction mixture was diluted with 25 ml of ethyl acetate and then washed with equal volumes of 0·5 N aqueous hydrochloric acid and distilled water to yield the dipeptide (**6**),† recrystallized from chloroform (87%), m.p. 209—211 °C; δ($CDCl_3$–CD_3SOCD_3) 1·07—2·23 (11 H, m, alkyl CH), 3·83 (2 H, d, *J* 6 Hz, CH_2), 5·06 (2 H, s, CH_2OCO), 5·51 (1 H, d, *J* 8 Hz, CH), and 7·27 (10 H, s, aryl)]. The peptide amide was homogeneous by t.l.c. on Merck $60F_{254}$ silica gel with 1% methanol in chloroform (R_F 0·17) or ethyl acetate (R_F 0·62) as eluant. Dibenzofulvene (**7**), the cleavage reaction by-product, was isolated as a white powder (79%), δ($CDCl_3$) 6·10 (2 H, s, $=CH_2$) and 7·23—7·87 (8 H, m, aryl)].



† Satisfactory analytical data were obtained for new compounds.

Other methods for removal of the *N*-fluoren-9-ylmethyl substituent proved less satisfactory. Treatment of (**5**) with ammonia-saturated methanol,[1] triethylamine–pyridine, or morpholine at room temperature for periods of 16 h did not result in substituent removal. Removal was possible by reaction of (**5**) in morpholine at 107 °C for 3·5 h to yield the dipeptide (**6**) (83%) and the dibenzofulvene–morpholine adduct (**8**) (81%), $\delta(CDCl_3)$ 2·60 (4 H, m, $[CH_2]_2N$), 2·63 (2 H, d, *J* 8 Hz, $CHCH_2N$), 3·80 (4 H, m, $[CH_2]_2O$), 4·03 (1 H, t, *J* 8 Hz, CH), and 7·17—7·80 (8H, m, aryl). Treatment of (**5**) with a catalytic amount of DBU (0·2 equiv.) in pyridine at room temperature for 72 h effected incomplete cleavage (*ca.* 90%).

The difficulties in cleaving the amide *N*-substituent can be overcome by utilizing 9-aminomethylfluorene (**2**) as the amine component in 4CC synthesis. The auxiliary group obtained in this approach can be efficiently removed under mild basic conditions. This procedure offers a means of cleaving the *N*-auxiliary group in 4CC synthesis which is complementary to methods required for the removal of common peptide blocking groups, *i.e.* benzyloxycarbonyl-, t-butyloxycarbonyl-, t-butyl ester, and 2-(biphenyl-4-yl)-isopropyloxycarbonyl-groups.

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