Synthesis of Isocyano Peptides by Dehydration of the *N*-Formyl Derivatives

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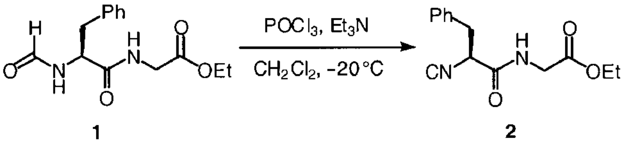
Abstract: Phosphoryl chloride in combination with triethylamine dehydrates *N*-formyl peptides to provide the corresponding isocyano peptides in excellent yields.

Key words: dehydration, *N*-formyl, isocyanide, isocyano peptide, phosphoryl chloride



1 2

Scheme 1

Isocyanides participate in a wide range of synthetically important transformations, mainly due to their profound ability to undergo α-addition with both electrophiles and nucleophiles.[1] The Ugi four-component[2] and Passerini[3] three-component reactions are notable examples that use this unique compound as a key input. Although a variety of isocyanides, including α-isocyano acetate[4] and tosyl methylisocyanide (TosMIC)[5] have been synthesized and widely used in organic syntheses, the chemistry of isocyano peptides remained underdeveloped. They have been synthesized by coupling of the α-isocyano acetic acid with C-terminal protected amino acids.[6] However, the yield was only low to moderate. Direct dehydration of *N*-formyl dipeptide with a large excess of tosyl chloride in pyridine[7] and with Burgess's reagent[8] have been reported in a sporadical case, without demonstrating the generality of the method. To the best of our knowledge, phosgene in combination with *N*-methyl morpholine[9] developed by Ugi and co-workers is the only general method for the dehydration of *N*-formyl dipeptides. However, the toxicity and cumbersome handling of phosgene may hamper its large-scale application.

In connection with our ongoing project aiming at the development of novel isocyanide-based multicomponent reactions,[10] we required a facile and reliable access to isocyano peptides.[11] After having screened various dehydrating agents, including triphosgene, *p*-TsCl/pyridine, Tf_2O/Hünig's base,[12] we found that easily available and cheap phosphoryl chloride[13] in combination with triethylamine is a mild and high-yielding alternative for the synthesis of α-isocyano peptide and report herein our results.

Treatment of a dichloromethane solution of *N*-formyl L-phenylalanine-glycine (**1**) with phosphoryl chloride (1.5 equiv) in the presence of triethylamine (5 equiv) at –20 °C provided the corresponding isocyano dipeptide **2** in 97% yield (Scheme 1). The procedure is applicable to other peptides with a variety of side chains and some representative examples were listed in Figure 1.

Since the combination of $POCl_3$/diisopropylamine was reported to cause the complete racemization of chiral methyl *N*-formylvalinate,[14] the extent of epimerization under the present conditions needed to be evaluated. Therefore, we synthesized the *N*-formyl L-phenylanine-L-phenylanine methyl ester (**3**) and its (L,D)-diastereomer **5**. Both compounds were smoothly converted to the corresponding isocyano derivatives **4** and **6** in 97% and 95% yield, respectively.[15] Analysis of the ^1H NMR spectra indicated that epimerization during the dehydration is less than 5%. Significantly, even with dipeptide **9** containing racemization-prone phenylglycine, the epimerization remained minimum. No chain-ring tautomerization leading to 5-aminooxazole occurred regardless of the nature of the internal amide bond (secondary or tertiary amide) thanks to the mild conditions used.[16] Extension of this chemistry to *N*-formyl tripeptide **19** was successful and isocyanide **20** was obtained in 95% yield. Partial decomposition of isocyanide **18** during purification was observed that might account for its reduced yield.

The reaction is easy to perform experimentally and all the isocyano peptides synthesized were odorless and can be purified by flash chromatography. The following procedure is typical. To a stirred solution of *N*-formylpeptide (2.0 mmol) and triethylamine (10.0 mmol) in dry CH_2Cl_2 (20.0 mL) cooled to –20 ºC was added drop wise the phosphoryl chloride (3.0 mmol) under argon. After being stirred at the same temperature for 2 hours, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness under reduce pressure. The crude residue was subjected to flash chromatography on silica gel to give the pure isocyanide.

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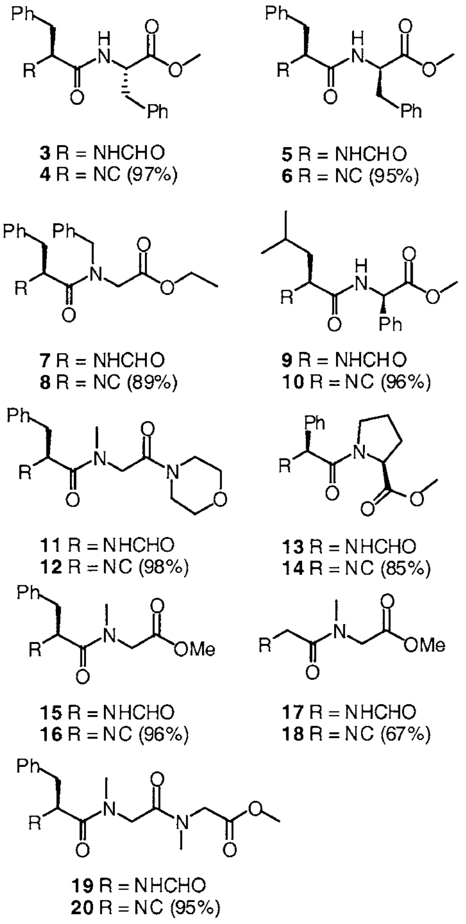

Figure 1

In conclusion, we have developed a reliable procedure for the synthesis of isocyano peptides from the corresponding *N*-formyl derivatives. Application of these isocyanides in diversity-oriented synthesis will be reported in due course.[17]

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(15) Compound **4**: $R_f = 0.43$ (EtOAc/heptane = 1/1); $[\alpha]_D = +13.8$ (*c* 0.3, $CHCl_3$). IR ($CHCl_3$): ν = 3422, 2138, 1744, 1684, 1603, 1522, 1497, 1437, 1363, 1180 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, ppm): δ = 3.08–3.30 (m, 4 H), 3.69 (s, 3 H,), 4.37 (dd, *J* = 4.5 Hz, 7.3 Hz, 1 H), 4.84 (dt, *J* = 5.7 Hz, 7.8 Hz, 1 H), 6.73 (d, *J* = 5.7 Hz, 1 H), 7.20–7.33 (m, 10 H). ^{13}C NMR (62.5 MHz, $CDCl_3$, ppm): δ = 37.6, 38.3, 52.4, 53.1, 59.4, 127.3, 127.6, 127.7, 129.6, 129.0, 134.4, 134.8, 164.1, 170.7. MS (EI): *m*/*z* = 336 (M^+), 227, 245. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.43; H, 5.95; N, 8.33. Found: C, 71.44; H, 5.98; N, 8.30. Compound **6**: $R_f = 0.48$ (EtOAc/heptane = 1/1.5); $[\alpha]_D = +17.5$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): ν = 3421, 3012, 2138, 1745, 1685, 1603, 1521, 1497, 1455, 1362, 1210, 1280, 1120 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, ppm): δ = 3.00–3.30 (m, 4 H), 3.72 (s, 3 H), 4.35 (dd, *J* = 4.2 Hz, 7.8 Hz, 1 H), 4.84 (dd, *J* = 6.7 Hz, 12.7 Hz, 1 H), 6.72 (d, *J* = 6.7 Hz, 1 H), 7.15–7.32 (m, 10 H). ^{13}C NMR (62.5 MHz, $CDCl_3$, ppm): δ = 37.8, 38.9, 52.6, 53.6, 59.9, 127.5, 127.8, 128.8, 129.2, 129.5, 134.7, 135.2, 164.7, 170.9. MS (EI): *m*/*z* = 336 (M^+), 277, 245. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.43; H, 5.95; N, 8.33. Found: C, 69.92; H, 6.05; N, 8.15.

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