A Modified U-4CR Reaction with 2-Nitrobenzylamine as an Ammonia Equivalent

Kuangsen Sung,* Fu-Lin Chen, Pei-Chun Huang

Department of Chemistry, National Cheng Kung University, Tainan, Taiwan
Fax +886(6)2740552; E-mail: kssung@mail.ncku.edu.tw

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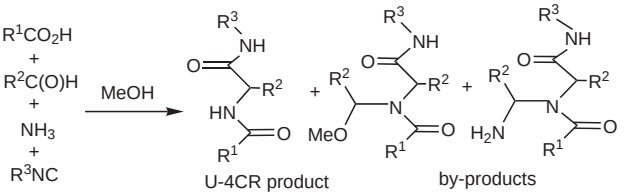
Abstract: A modified U-4CR reaction has been done by using commercially available 2-nitrobenzylamine as an ammonia equivalent and it involves a multi-component reaction, followed by photochemical cleavage of the 2-nitrobenzyl group, which can be done in one pot with good yields.

Key words: multicomponent reaction, photochemistry, peptides, isocyanide, ammonia equivalent



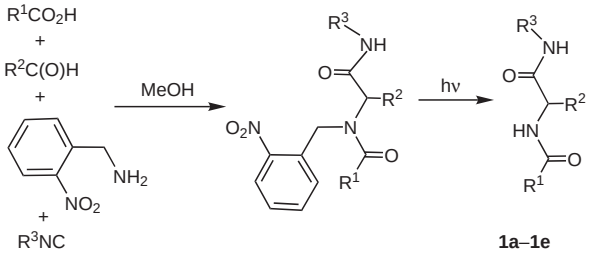
Scheme 1

The U-4CR reaction, invented by Ugi in 1959,[1] is one of many useful multi-component reactions.[2] It consists of four components: amine, carboxylic acid, aldehyde, and isocyanide. A variety of the four components allows the U-4CR reaction to produce various interesting structures[2] including biologically active benzodiazepines,[3] unnatural peptide fragments,[4] cyclopeptides,[5] and PNA.[6]

Incorporation of an unnatural peptide into a bioactive peptide framework often increases bioactivity, bioavailability, and degradative resistance.[7] The U-4CR is able to prepare the unnatural peptides. To mimic the natural peptides, the amine component of the U-4CR reaction has to be ammonia. However, very few examples of the U-4CR reaction used ammonia as the amine component.[8] Recently, Kazmaier characterized the by-products of the U-4CR reaction with ammonia as the amine component[9a] (Scheme 1), and the problem was solved by a less nucleophilic solvent of trifluoroethanol or hydrolysis of the by-products with pyridinium *p*-toluenesulfonate (PPTS).[9b] No wonder several attempts have been undertaken to solve these problems by using primary amines as the amine component, whose auxiliaries can be cleaved under acidic conditions after the U-4CR reaction.[10,11] The most successful primary amine used for this purpose is a carbohydrate with an amino group at the anomeric position, and the carbohydrate can been removed under acidic conditions after the U-4CR.[12] This method has been used to prepare chiral α-amino acids with high stereoselectivity, but it takes several steps to prepare the chiral 1-amino-glucopyranoses.[12]

In this communication, we used commercially available 2-nitrobenzylamine as the amine component in the U-4CR reaction, and cleaved the 2-nitrobenzyl group photochemically after the reaction (Scheme 2). This design allows the two-step processes to be carried out in one pot without the isolation of the stable intermediate and adding any other reagent.

According to the U-4CR,[2] we mixed commercially available 2-nitrobenzylamine hydrochloride with isocyanide, aldehyde, and carboxylic acid components in methanol at room temperature, but the product we obtained was a P-3CR product.[2] Free base of 2-nitrobenzylamine, which was generated by neutralization of 2-nitrobenzylamine hydrochloride with sodium carbonate, was treated with isocyanide, aldehyde, and carboxylic acid components in methanol at room temperature and the expected U-4CR product was produced (Scheme 2).



1a: R^1 = Ph, R^2 = *i*-Pr, R^3 = *p*-MeC_6H_4
1b: R^1 = *n*-Pr, R^2 = *m*-BrC_6H_4, R^3 = *c*-Hex
1c: R^1 = Ph, R^2 = Ph, R^3 = *c*-Hex
1d: R^1 = Boc-$NHCH_2$, R^2 = *i*-Pr, R^3 = cyclohexenyl
1e: R^1 = Me, R^2 = *n*-Pr, R^3 = *p*-MeC_6H_4

Scheme 2

After the U-4CR product with a 2-nitrobenzylamine moiety was subjected to irradiation at λ = 254 nm in methanol for 6–13 hours, and the 2-nitrobenzyl group was successfully cleaved off from the U-4CR product. The reaction progress was monitored by ^{1}H NMR spectroscopy, and longer reaction time diminished the yield.

To find out if this method can be applied to various U-4CR reactions, various carboxylic acid, aldehyde, and isocyanide components with aromatic, alkyl, bulky, or

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Table 1 Syntheses of Dipeptides **1a–e** by the U-4CR Reactions, Followed by Photochemical Cleavage of 2-Nitrobenzyl Group (Scheme 2)

R^1	R^2	R^3	Product (yield)
Ph	*i*-Pr	*p*-MeC_4H_6	**1a** (93%)
n-Pr	*m*-BrC_6H_4	*m*-BrC_6H_4	**1b** (84%)
Ph	Ph	*c*-Hex	**1c** (89%)
Boc-$NHCH_2$	*i*-Pr	*c*-Hex	**1d** (68%)
Me	*n*-Pr	*p*-MeC_6H_4	**1e** (91%)

functional substituents were used in the U-4CR reactions. The U-4CR reactions, followed by photochemical cleavage of 2-nitrobenzyl group were done in one pot without isolation of the stable U-4CR products. As shown in Table 1, they all worked fine with good yields.[13]

In conclusion, we successfully modified the U-4CR with commercially available 2-nitrobenzylamine as the ammonia equivalent. This method can be done in one pot with high yields.

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(13) The general procedure of this method is shown as follows: An aldehyde component (1 mmol), 2-nitrobenzylamine (1 mmol), and MeOH (5 mL) were mixed in a 10-mL quartz flask until the mixture became a clear solution. An isocyanide component (1 mmol) and a carboxylic acid component (1 mmol) were added into the solution and the mixture was stirred at r.t. for 2 d. Then the mixture was irradiated in a quartz flask inside a Rayonet photochemical reactor with four 254-nm lamps at r.t. The reaction was monitored by ^{1}H NMR spectroscopy, and the reaction was complete in 6–13 h. After the reaction was completed, MeOH was removed by a rotary evaporator, and the residue was purified by column chromatography to get the dipeptides **1a**–**1e**.
1a: Light brown solid; mp 119 °C; yield: 93%. ^{1}H NMR (CD_3OD): δ = 0.94 (d, *J* = 7.6 Hz, CH_3, 3 H), 0.96 (d, *J* = 7.6 Hz, CH_3, 3 H), 2.14–2.15 (m, 1 H, CH), 2.20 (s, 3 H, CH_3), 4.37 (d, *J* = 8.4 Hz, CH, 1 H), 7.06 (d, *J* = 8.2 Hz, PhH, 2 H), 7.44–7.47 (m, 5 H, PhH), 7.84 (d, *J* = 8.2 Hz, PhH, 2 H). ^{13}C NMR ($CDCl_3$): δ = 19.46, 19.74, 20.83, 31.19, 60.81, 120.39, 128.23, 129.00, 129.81, 132.12, 133.55, 134.95, 136.82, 167.98, 171.04. IR (thin film): 1654, 1642 (C=O) cm^{-1}.
1b: Brown oil; yield: 84%. ^{1}H NMR ($CDCl_3$): δ = 0.89 (d, *J* = 7.2 Hz, CH_3, 3 H), 1.22 (m, 2 H, CH_2), 1.27–1.29 (m, 4 H, CH_2), 1.55–1.57 (m, 2 H, CH_2), 1.67–1.69 (m, 4 H, CH_2), 2.18 (t, *J* = 7.4 Hz, CH_2, 2 H), 3.56–3.58 (m, 1 H, CH), 5.37 (s, 1 H, CH), 7.22–7.26 (m, 1 H, PhH), 7.34–7.36 (m, 1 H, PhH), 7.41–7.43 (m, 1 H, PhH), 7.57 (s, 1 H, PhH). ^{13}C NMR ($CDCl_3$): δ = 16.45, 22.75, 28.51, 28.56, 29.07, 35.95, 36.08, 41.00, 60.39, 125.96, 129.70, 133.84, 134.65, 135.41, 144.43, 173.31, 178.13. IR (thin film): 1649, 1634 (C=O) cm^{-1}.
1c: Red brown oil; yield: 89%. ^{1}H NMR ($CDCl_3$): δ = 1.22–1.27 (m, 4 H, CH_2), 1.27–1.29 (m, 2 H, CH_2), 1.66–1.70 (m, 4 H, CH_2), 3.67–3.69 (m, 1 H, CH), 5.63 (s, 1 H, CH), 7.36–7.39 (m, 3 H, PhH), 7.49 (d, 2 H, PhH), 7.63–7.66 (m, 2 H, PhH), 7.75–7.79 (m, 1 H, PhH), 8.10–8.14 (m, 2 H, PhH). ^{13}C NMR ($CDCl_3$): δ = 26.06, 26.12, 26.63, 33.50, 33.66,

50.15, 59.25, 125.49, 128.76, 129.32, 129.76, 130.41, 131.88, 133.69, 135.05, 138.63, 147.81, 168.95, 171.14. IR (thin film): 1650, 1629 (C=O) cm^{-1}.

1d: Light yellow oil; yield: 68%. ^1H NMR (CD_3OD): δ = 0.92 (d, *J* = 6.9 Hz, CH_3, 3 H), 0.95 (d, *J* = 6.9 Hz, CH_3, 3 H), 1.44 (s, 9 H, CH_3), 1.64–1.66 (m, 2 H, CH_2), 1.73–1.75 (m, 2 H, CH_2), 1.85–1.87 (m, 1 H, CH), 2.10–2.12 (m, 4 H, CH_2), 3.77–3.79 (m, 2 H, CH_2), 4.22 (dd, *J* = 7.8, 8.1 Hz, 1 H, CH), 5.29 (t, *J* = 5.4 Hz, 1 H, CH). ^{13}C NMR ($CDCl_3$): δ = 19.24, 25.41, 26.99, 28.25, 29.68, 32.72, 41.96, 44.60, 57.93, 80.59, 97.23, 124.10, 156.32, 169.91, 173.55. IR (thin film): 1701, 1672, 1648 (C=O) cm^{-1}.

1e: Red brown oil; yield: 89%. ^1H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, CH_3, 3 H), 1.39–1.41 (m, 2 H, CH_2), 1.68–1.70 (m, 1 H, CH_2), 1.88–1.90 (m, 1 H, CH_2), 2.02 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 4.59 (q, *J* = 6.9 Hz, 1 H, CH), 7.09 (d, *J* = 8.4 Hz, 2 H, PhH), 7.41 (d, *J* = 8.4 Hz, 2 H, PhH). ^{13}C NMR ($CDCl_3$): δ = 13.78, 18.89, 20.85, 23.18, 34.30, 53.84, 120.01, 129.41, 134.06, 135.16, 170.01, 170.69. IR (thin film): 1679, 1651 (C=O) cm^{-1}.