J IRAN CHEM SOC (2014) 11:85–90
DOI 10.1007/s13738-013-0278-5

ORIGINAL PAPER

Participation of ethyl 3-formylindole-2-carboxylate with the Ugi four-component condensation reaction

Morteza Shiri · Mohammad Ali Zolfigol · Ardeshir Khazaei · Toktam Faal-Rastegar · Hendrik G. Kruger

Received: 31 October 2012 / Accepted: 22 May 2013 / Published online: 7 June 2013

Abstract Multicomponent condensation of ethyl 3-formylindole 2-carboxylate, amines, isocyanide and (S)-*N*-boc-alanine or (S)-*N*-boc-serine is described. This Ugi four-component condensation (Ugi-4CC) reaction yielded a series of novel dipeptides containing an indolyl moiety. These compounds exhibit potential biological activity.

Keywords Condensation · Dipeptides · Indole · Multicomponent reactions · Amines

Introduction

Both naturally occurring and also synthetic derivatives of indole gained much attention of chemists due to their various biological activities, medicinal uses, and agriculture applications, etc. [1, 2].

Therefore, many reports on the synthesis of new analogues of indole and also the modification of existing procedures for the synthesis of related compounds have appeared [3–5].

In this context one of the top findings of organic chemists in the past two decades is the development of multicomponent synthesis of organic compounds. These methods are also attractive since it is more economical than conventional methods, it produces minimal waste and it is less time consuming. This technique was regenerated by Ugi and can be defined as: a one-pot reaction where more than two reactants are combined in a reaction vessel to form a product containing of most of the atoms in the starting materials [6–8]. A large diversity of indoles that are difficult to prepare with classical methods, have easily been prepared using this technique [9].

The multicomponent reaction of an amine, aldehyde, isocyanide and acid is known as an Ugi four-component condensation (Ugi-4CC) reaction. This mixture yields a diamide as major product. Participation of *N*-protected amino acids in this reaction leads to the formation of dipeptides. Domling and co-workers [10] synthesized aspergillamide analogues (containing an indole moiety) via this method and evaluated their antibiotic and cytotoxic activities. They reported several of them that were more potent than the natural analogues. Waki and Meienhofer [11] used *N*-protected glycine in an Ugi-4CC reaction in the synthesis of indolyl dipeptides. A patent disclosed active bioisosteres of the antibiotic actinoin utilizing a similar Ugi-4CC approach [12].

Experimental section

General

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. IR spectra were acquired on a Shimadzu Infra-Red Spectroscopy IR-435. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 Spectrometer in d_6-DMSO or $CDCl_3$ as

M. Shiri (✉)
Department of Chemistry, Faculty of Science, Alzahra University, Vanak, 1993893973 Tehran, Iran
e-mail: mshiri@alzahra.ac.ir

M. A. Zolfigol (✉) · A. Khazaei · T. Faal-Rastegar
Faculty of Chemistry, Bu-Ali Sina University, 6517838683 Hamedan, Iran
e-mail: Iranzolfi@basu.ac.ir

H. G. Kruger
Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban 4001, South Africa

solvent. A Leco CHNS, model 932 was used for elemental analysis.

General procedures

Ugi-4CC of ethyl 3-formylindole-2-carboxylate, amines, isocyanide and (S)-*N*-boc-alanine or (S)-*N*-boc-serine.

A solution of 3-formylindole-2-carboxylate (1 mmol) and the amine (1 mmol) in methanol (5 mL) was stirred for 30 min at room temperature and then the amino acid (1 mmol) and isocyanide (1 mmol) were added. The reaction was stopped after 48 h and the solvent was evaporated. The residue was purified by column chromatography using *n*-hexane-ethyl acetate as eluent.

Physical and spectral data for the products:

3a: white powder with mp: 253 °C.

FT-IR (KBr): 3,334, 2,916, 1,608, 1,544, 1,430, 1,129 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.12 (3 H, d, $J = 6.76$ Hz), 1.27–1.36 (5 H, m), 1.38 (3 H, t, $J = 7.11$ Hz), 1.45 (9 H, s), 1.61 (2 H, m), 1.74 (1 H, m), 1.87 (1 H, m), 2.05 (1 H, m), 2.18 (3 H, s), 3.91 (1 H, m), 4.16 (1 H, m), 4.35 (1 H, m), 4.45 (1 H, m), 5.36 (1 H, s), 6.10 (1 H, s, br), 6.27 (1 H, s, br), 6.50 (1 H, s, br), 6.78 (1 H, t, $J = 7.52$ Hz), 7.06 (3 H, t, $J = 7.29$ Hz), 7.12 (1 H, d, $J = 8.36$ Hz), 7.26 (1 H, m), 7.72 (1 H, s, br), 9.45 (1 H, s, br).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.7, 18.9, 21.2, 25.3, 25.5, 25.8, 28.8, 33.1, 33.2, 47.8, 49.3, 49.4, 56.8, 62.0, 79.7, 111.9, 115.5, 120.8, 122.2, 125.5, 126.3, 127.5, 128.8, 130.2, 135.7, 135.8, 136.2, 138.4, 162.2, 168.5, 173.8.

Anal. Calcd. for: $C_{34}H_{44}N_4O_6$, C, 67.53; H, 7.33; N, 9.26; Found C, 67.44; H, 7.29; N, 9.17.

3b: white powder with mp: 207 °C.

FT-IR (KBr): 3,365, 2,976, 1,715, 1,655, 1,525, 1,253, 1,174, 743 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.14 (5 H, m), 1.34 (3 H, m), 1.44 (12 H, m), 1.62 (2 H, m), 1.77 (2 H, m), 1.88 (2 H, m), 2.06 (1 H, m), 2.26 (1 H, m), 3.93 (1 H, m), 4.18 (1 H, m), 4.40 (1 H, m), 4.46 (1 H, m), 5.35 (1 H, s), 5.96 (1 H, m), 6.21 (1 H, s, br), 6.79 (2 H, d, $J = 12.37$), 7.06-7.33 (5 H, m), 7.63 (1 H, s, br), 9.31 (1 H, s, br).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.8, 25.4, 25.6, 25.9, 28.8, 33.2, 33.3, 49.4, 62.1, 79.7, 120.6, 122.3, 125.6, 129.2, 135.8, 138.8, 162.3.

Anal. Calcd. for: $C_{34}H_{44}N_4O_6$, C, 67.53; H, 7.33; N, 9.26; Found C, 67.62; H, 7.41; N, 9.18.

3c: white powder with mp: 235 °C.

FT-IR (KBr): 3,335, 2,976, 1,705, 1,640, 1,513, 1,233 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.01 (5 H, m), 1.27–1.43 (13 H, m), 1.59 (2 H, m), 1.71 (1 H, m), 1.84 (1 H, m), 2.01 (1 H, m), 2.18 (2 H, m), 3.86 (1 H, m), 4.16 (1 H, m), 4.33 (1 H, m), 4.40 (1 H, m), 4.67 (1 H, m), 5.40 (1 H, s), 5.99 (1 H, s, br), 6.10 (1 H, d, $J = 6.41$ Hz), 6.28 (1 H, s), 6.59 (1 H, d, $J = 7.36$ Hz), 6.60 (1 H, m), 7.07 (2 H, m), 7.18 (2 H, m), 7.55 (1 H, d, $J = 7.33$ Hz), 8.11 (1 H, s, br), 9.66 (1 H, s, br).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.7, 18.9, 25.3, 25.5, 25.8, 28.9, 33.1, 33.2, 47.9, 49.5, 57.1, 61.9, 80.0, 112.1, 115.1, 115.4, 116.3, 121.0, 122.2, 125.6, 126.5, 135.9, 157.1, 162.2, 168.9.

Anal. Calcd. for: $C_{33}H_{42}N_4O_7$ C, 65.33; H, 6.98; N, 9.23; Found C, 65.41; H, 7.15; N, 9.34.

3d: white powder with mp: 229 °C.

FT-IR (KBr): 3,392, 3,261, 2,935, 1,699, 1,650, 1,513, 1,246, 746 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.19 (4 H, m), 1.30–1.44 (16 H, m), 1.61 (2 H, m), 1.73 (1 H, m), 1.82 (1 H, m), 2.04 (1 H, m), 3.60 (3 H, s), 3.91 (1 H, m), 4.17 (1 H, m), 4.36 (1 H, m), 4.43 (1 H, m), 5.39 (1 H, s), 6.10 (1 H, s, br), 6.18 (1 H, s, br), 6.20 (1 H, s, br), 6.77 (2 H, m), 7.07 (2 H, m), 7.11 (1 H, m), 7.26 (1 H, m), 7.79 (1 H, m), 9.49 (1 H, s, br).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.8, 19.0, 25.4, 25.6, 25.9, 28.9, 33.2, 33.4, 47.9, 49.4, 55.7, 56.9, 62.0, 79.7, 112.0, 113.8, 114.5, 115.6, 120.9, 122.1, 125.6, 126.4, 127.6, 131.5, 132.3, 135.9, 155.6, 159.5, 162.2, 168.7, 174.0.

Anal. Calcd. for: $C_{34}H_{44}N_4O_7$ C, 65.79; H, 7.14; N, 9.03; Found C, 65.68; H, 7.22; N, 9.12.

3e: white powder with mp: 225 °C.

FT-IR (KBr): 3,390, 3,251, 2,934, 1,684, 1,654, 1,515, 1,245, 748 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.08–1.13 (5 H, m), 1.31-1.44 (15 H, m), 1.60 (2 H, m), 1.72 (1 H, m), 1.84 (1 H, m), 2.02 (1 H, m), 3.90 (1 H, m), 4.13 (1 H, m), 4.38 (1 H, m), 4.45 (1 H, m), 5.38 (1 H, s), 6.15 (2 H, s, br), 6.67 (1 H, m), 6.82 (1 H, t, $J = 7.31$ Hz), 7.09 (3 H, m), 7.25 (2 H, m), 7.87 (1 H, s, br), 9.55 (1 H, s, br).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.8, 19.1, 25.4, 25.5, 25.8, 28.8, 33.2, 33.3, 47.9, 49.5, 56.8, 62.1, 79.9, 112.2, 115.0, 121.2, 121.7, 125.8, 126.4, 127.3, 128.3, 129.9, 134.6, 135.9, 137.5, 162.0, 168.5, 173.5.

Anal. Calcd. for: $C_{33}H_{41}ClN_4O_6$ C, 63.40; H, 6.61; N, 8.96; found C, 63.30; H, 6.54; N, 9.11.

3f: white powder with mp: 144 °C.

FT-IR (KBr): 3,348, 2,977, 1,698, 1,662, 1,512, 1,251, 745 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.11 (3 H, d, $J = 6.75$ Hz), 1.35–1.41 (21 H, m), 2.09 (3 H, s),

4.18 (1 H, m), 4.31 (1 H, m), 4.35 (1 H, m), 5.48 (1 H, s), 5.95 (1H, s, br), 6.08 (1 H, m), 6.60 (1 H, m), 6.77 (1 H, t, $J = 7.60$ Hz), 7.12 (3 H, m), 7.22 (1 H, m), 7.23 (1 H, m), 7.74 (1 H, m), 9.71 (1 H, s).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.7, 19.3, 21.2, 28.8, 29.1, 47.9, 52.1, 57.6, 62.0, 79.6, 112.0, 115.6, 120.8, 122.5, 125.6, 126.4, 127.4, 128.8, 130.2, 131.1, 135.9, 136.2, 138.4, 155.4, 162.4, 168.7, 173.9.

Anal. Calcd. for: $C_{32}H_{42}N_4O_6$ C, 66.41; H, 7.32; N, 9.68; Found C, 66.29; H, 7.24; N, 9.72.

3g: white powder with mp: 215 °C.

FT-IR (KBr): 3,355, 2,981, 1,661, 1,246 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.12 (3 H, d, $J = 6.70$ Hz), 1.26–1.42 (21 H, m), 3.61 (3 H, s), 4.20 (1 H, m), 4.34 (1 H, m), 4.42 (1 H, m), 5.50 (1 H, m), 5.90 (1H, s), 6.12 (1 H, m), 6.18 (1 H, m), 6.77 (2 H, m),7.09 (2 H, m), 7.23 (1 H, m), 7.24 (1 H, m), 7.81 (1 H, m), 9.64 (1 H, s, br).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.7, 19.3, 28.8, 29.1, 47.9, 52.1, 55.7, 57.4, 62.1, 79.6, 112.0, 113.8, 114.4, 115.6, 120.9, 122.5, 125.7, 126.4, 127.5, 131.6, 132.5, 135.9, 155.4, 159.5, 162.4, 168.8, 174.0.

Anal. Calcd. for: $C_{32}H_{42}N_4O_7$ C, 64.63; H, 7.12; N, 9.42; Found C, 64.55; H, 7.24; N, 9.35.

3h: white powder with mp: 148 °C.

FT-IR (KBr): 3,417, 3,362, 2,975, 1,683, 1,662, 1,492, 1,254, 747 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.13 (3 H, d, $J = 6.74$ Hz), 1.33 (9 H, s), 1.41 (12 H, m), 4.17 (1 H, m), 4.37 (1 H, m), 4.45 (1 H, m), 5.47 (1 H, d, $J = 6.63$ Hz), 5.75 (1 H, s), 6.19 (1 H, m), 6.71 (1 H, m), 6.84 (1 H, t, $J = 7.60$ Hz), 7.14 (3 H, m), 7.28 (2 H, m), 7.91 (1 H, s), 9.54 (1 H, s, br).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.7, 19.3, 20.9, 21.4, 28.7, 29.0, 47.9, 51.8, 57.4, 61.6, 79.3, 112.3, 120.1, 122.1, 125.0, 126.6, 127.5, 127.8, 128.9, 129.2, 131.2, 136.2, 138.7, 162.3.

Anal. Calcd. for: $C_{31}H_{39}ClN_4O_6$ C, 62.15; H, 6.56; N, 9.35; Found C, 62.21; H, 6.47; N, 9.23.

3i: white powder with mp: 253 °C.

FT-IR (KBr): 3,372, 2,980, 1,645, 1,244 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.16 (3 H, d, $J = 6.74$ Hz), 1.35 (9 H, s), 1.50 (12 H, m), 4.18 (1 H, m), 4.47 (1 H, m), 4.50 (1 H, m), 5.41 (1 H, s), 5.69 (1 H, m), 6.30 (1 H, m), 6.61 (1 H, m), 6.87 (1 H, m), 7.20 (4 H, m), 7.89 (1 H, m), 8.17 (1 H, m), 9.19 (1 H, s, br).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm):

Anal. Calcd. for: $C_{31}H_{39}BrN_4O_6$ C, 57.85; H, 6.11; N, 8.71; Found C, 57.91; H, 6.21; N, 8.55.

3j: white powder with mp: 253 °C.

FT-IR (KBr): 3,380, 2,976, 1,712, 1,650, 1,523, 1,255 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.03 (3 H, d, $J = 6.70$ Hz), 1.22–1.50 (21 H, m), 1.35 (10 H, m), 4.17 (1 H, m), 4.28 (2 H, m), 5.39 (1 H, m), 5.75 (1H, s, br), 6.83 (1 H, m), 7.07 (2 H, m), 7.17 (2 H, m), 7.32 (4 H, m), 7.45 (1 H, m), 7.59 (2 H, m), 7.84 (1 H, d, $J = 6.81$ Hz) 7.99 (1 H, m), 8.93 (1 H, s).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.6, 19.9, 28.8, 29.1, 48.1, 52.0, 58.6, 62.0, 79.5, 111.6, 115.1, 121.0, 123.2, 123.6, 125.7, 126.0, 126.1, 126.4, 127.0, 128.2, 129.5, 129.8, 131.8, 134.3, 135.7, 136.1, 162.1, 168.0.

Anal. Calcd. for: $C_{35}H_{42}N_4O_6$ C, 68.38; H, 6.89; N, 9.11; Found C, 68.29; H, 6.83; N, 9.25.

3k: white powder with mp: 120 °C.

FT-IR (KBr): 3,440, 3,360, 2,976, 1,715, 1,686, 1,453, 1,175, 779 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 0.37 (3 H, d, $J = 6.39$ Hz), 0.73 (3H, d, $J = 6.55$ Hz) 1.07 (2 H, m), 1.25-1.66 (20 H, m), 2.10 (4 H, m), 3.90 (1 H, m), 4.19 (1 H, m), 4.34 (1 H, m), 4.39 (1 H, m), 5.20 (1 H, s), 5.82 (1 H, s, br), 6.36 (1 H, m), 6.49 (1 H, m), 6.74 (1 H, m), 7.06 (3H, m), 7.29 (1 H, m), 7.30 (1 H, m), 7.72 (1 H, m), 9.57 (1 H, s).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.7, 21.1, 21.3, 23.8, 24.8, 25.4, 25.6, 25.9, 28.8, 33.2, 33.3, 42.2, 49.4, 50.6, 56.7, 62.0, 79.7, 112.0, 115.7, 120.8, 122.2, 125.5, 126.4, 127.7, 128.6, 130.3, 130.5, 131.1, 135.9, 136.1, 138.4, 156.1, 162.3, 168.7, 173.9.

Anal. Calcd. for: $C_{37}H_{50}N_4O_6$ C, 68.71; H, 7.79; N, 8.66; Found C, 68.68; H, 7.74; N, 8.45.

3l: white powder with mp: 145 °C.

FT-IR (KBr): 3,445, 2,921, 1,671, 1,241 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 0.37 (3 H, d, $J = 6.35$ Hz), 0.73 (3H, d, $J = 6.61$ Hz) 1.27-1.48 (24 H, m), 2.11 (3 H, s), 4.22 (1 H, m), 4.41 (2 H, m), 5.23 (1 H, m), 6.04 (1 H, m), 6.11 (1 H, m), 6.50 (1 H, m), 6.76 (1 H, t, $J = 7.4$ Hz) 7.08 (3H, m), 7.19 (2 H, m), 7.73 (1 H, m), 9.58 (1 H, s).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.7, 21.1, 21.3, 23.8, 24.9, 28.8, 29.1, 42.5, 50.7, 52.0, 57.4, 62.0, 79.6, 111.9, 115.9, 120.7, 122.6, 125.5, 126.4, 127.6, 128.6, 130.5, 135.9, 136.2, 138.4, 162.4, 168.7, 173.9.

Anal. Calcd. for: $C_{35}H_{48}N_4O_6$ C, 67.72; H, 7.79; N, 9.03; Found C, 67.82; H, 7.71; N, 9.13.

3m: white powder with mp: 122 °C.

FT-IR (KBr): 3,455, 2,954, 1,634, 1,229 cm^{-1}.

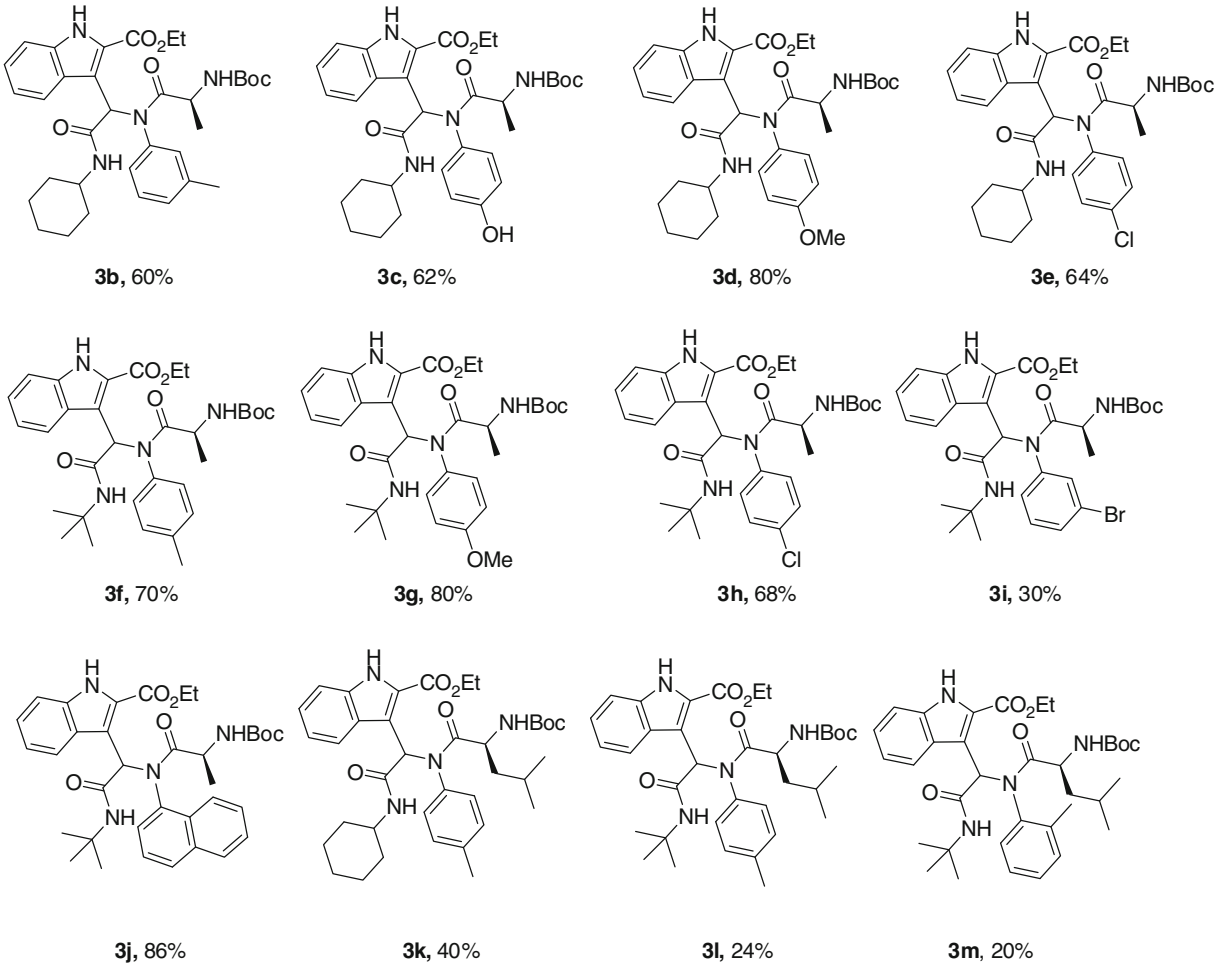
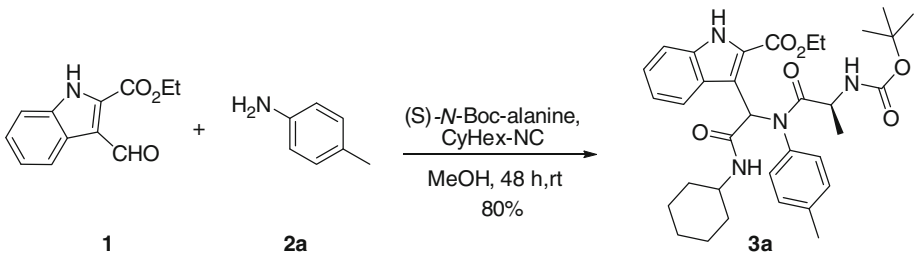


Fig. 1 Indolyl dipeptides

Scheme 1 Ugi 4-CC of ethyl 3-formylindole-2-carboxylate 1



^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 0.45 (3 H, d, $J = 5.58$ Hz), 0.78 (3H, d, $J = 6.51$ Hz) 1.35 (11 H, m), 1.43 (12 H, m), 1.73 (3 H, s), 4.17 (1 H, m), 4.39 (1 H, m), 4.45 (1 H, m), 5.12 (1 H, s), 5.81 (1 H, m), 6.81 (2H, m), 7.04 (1H, m), 7.15 (2 H, m), 7.28 (2 H, m), 7.69 (1 H, m), 9.17 (1 H, s).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.7, 17.8, 21.4, 23.9, 24.8, 28.8, 29.1, 50.6, 51.9, 57.7, 62.0, 111.7, 121.0, 123.7, 125.8, 126.8, 127.3, 129.1, 131.0, 132.4, 135.8, 162.1.

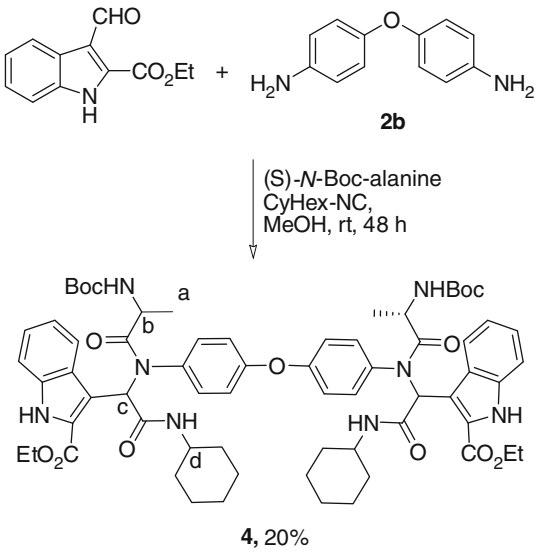
Anal. Calcd. for: $C_{35}H_{48}N_4O_6$ C, 67.72; H, 7.79; N, 9.03; Found C, 67.65; H, 7.66; N, 8.91.

4: white powder with mp: 210 °C.

FT-IR (KBr): 3,429, 2,981, 1,644, 1,242 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.10 (2 H, m), 1.16 (6H, d, $J = 6.66$ Hz) 1.32–1.9 (40 H, m), 2.11 (2 H, m), 3.98 (1 H, m), 4.20 (1 H, m), 4.43 (1 H, m), 4.45 (1 H, m), 5.32 (1 H, m), 5.86 (1 H, m), 6.07 (1 H, m), 6.27 (1H, m), 6.42 (1 H, m), 6.53 (1 H, m), 6.70 (1 H, m), 6.73 (1 H, m), 6.90 (1 H, m), 7.10 (1H, m), 7.19 (1 H, m), 7.81 (1 H, m), 9.17 (1 H, s).

^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 14.8, 19.4, 28.8, 29.1, 47.9, 52.2, 57.4, 62.2, 79.8, 112.1, 115.1, 121.2,



Scheme 2 Ugi 4-CC of diamine **2b**

122.2, 126.0, 126.4, 127.2, 128.3, 131.7, 134.7, 135.9, 137.5, 155.4, 162.1, 168.4.

Anal. Calcd. for: $C_{66}H_{82}N_8O_{13}$ C, 66.31; H, 6.91; N, 9.37; Found C, 66.33; H, 6.78; N, 9.30.

Results and discussion

To the best of our knowledge, complex amino acids have not been employed in the synthesis of indolyl containing dipeptides. With this in mind, we chose (S)-*N*-boc-alanine or (S)-*N*-boc-serine as acid sources in a similar Ugi reaction.

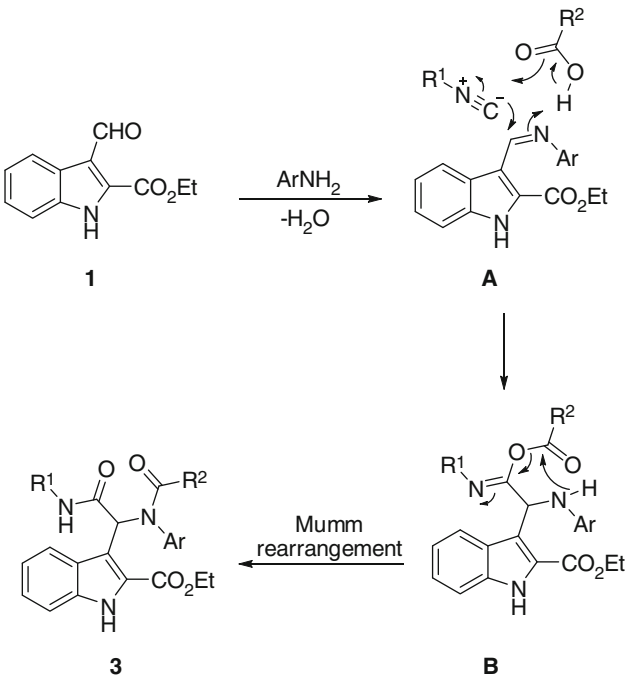
In the first step 3-formylindole 2-carboxylate, *p*-toluidine, cyclohexyl isocyanide (CyHex-NC) and (*S*)-*N*-boc-alanine were condensed in methanol at room temperature to yield the dipeptide **3a** in 80 % after 48 h (Scheme 1). Compound **3a** was formed as a mixture of two diastereomers (1:1). Both methanol and ethanol were used at room temperature as well as under reflux conditions, giving similar yields. Since this family of molecules is novel and is suspected to exhibit potentially biological activity, we used the same process to prepare a series of related derivatives.

As it can be seen in Fig. 1, aniline derivatives including electron donating and electron withdrawing groups were successfully introduced to this condensation and the corresponding indoles **3b–d** have been isolated in moderate yields. When *tert*-butyl isocyanide instead of CyHex-NC was used compounds **3f–j** were isolated.

Serine derivatives **3k–m** were isolated in low to moderate yield (between 20 and 40 %) most possibly due to increased steric hindrance (Fig. 1).

The more complex compound **4** was obtained when we used the diamine **2b** in reaction with 3-formylindole-2-carboxylate, CyHex-NC and (*S*)-*N*-boc-alanine (Scheme 2). The yield is possibly suppressed due to steric effects and also as result of the deactivation of the indolic formyl group through resonance from the indole nitrogen lone pair. The structure of compound (**4**) was established on the basis of spectroscopic data. In the IR spectrum, stretching frequencies at 1,644 and 3,429 cm^{-1} confirmed the presence of C=O and N–H functional groups, respectively. The ^1H NMR spectrum showed a broad distinct singlet in the region of δ 9.17 and two doublets in δ 6.27 and 5.33 corresponding to the NH proton, respectively, to indole, amide and carbamate (D_2O exchangeable). The aromatic proton resonated in the region of δ 6.42–7.81. Protons in related to CH_b and CH_d were appeared as multiplet in δ 4.19 and 4.50 and a singlet for CH_c in δ 5.86 (Scheme 2). Aliphatic protons related to CH_3 and CH_2 were appeared from δ 1.1 to 2.1. In the ^{13}C NMR spectrum, the apparent 9 signals in aliphatic area and 15 signals from 112.1 to 168.4 indicated a symmetrical structure for the molecule.

A plausible reaction mechanism is shown in Scheme 3. Imine **A** which came from aldehyde **1** and amine, reacted with isocyanide and acid to form intermediate **B**. The latter through Mumm rearrangement by transfer of acyl group from oxygen to nitrogen gave product **3** (Scheme 3).



Scheme 3 A plausible mechanism

Conclusion

In summary, we have prepared a novel family of indolyl dipeptides using the Ugi condensation between

3-formylindole-2-carboxylate, amines, isocyanides and *N*-boc-amino acids. These products which potentially may exhibit biological activity were isolated as a mixture of inseparable diastereomers.

Acknowledgments We thank Alzahra University and Bu-Ali Sina University and also National Elites Fundation (Iran) for financial support to our research group.

References

1. J.A. Joule, In Science of Synthesis; E. J. Thomas, Ed.; Georg Thieme Verlag: Stuttgart, New York, 2000; Vol. 10, pp. 361–652
2. R.J. Sundberg, *Indoles* (Academic Press, London, 1996)
3. G.R. Humphrey, J.T. Kuethe, Chem. Rev. **106**, 2875 (2006)
4. S. Cacchi, G. Fabrizi, Chem. Rev. **105**, 2873 (2005)
5. M. Shiri, M.A. Zolfigol, H.G. Kruger, Z. Tanbakouchian, Chem. Rev. **110**, 2550 (2010)
6. A. Domling, I. Ugi, Angew. Chem. Int. Ed. **39**, 3168 (2000)
7. A. Domling, Chem. Rev. **106**, 17 (2006)
8. J. Zhu, H. Bienaym, *Multicomponent Reactions.* Wiley-VCH: Weinheim, Germany, 2005
9. M. Shiri, Chem. Rev. **112**, 3508 (2012)
10. B. Beck, S. Hess, A. Domling, Bioorg. Med. Chem. Lett. **10**, 1701 (2000)
11. M. Waki, J. Meienhofer, J. Am. Chem. Soc. **98**, 6075 (1977)
12. M. Thormann, M. Almstetter, US2007/0060624(A1)