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A new and versatile one-pot synthesis of indol-2-ones by a novel Ugi-four-component-Heck reaction

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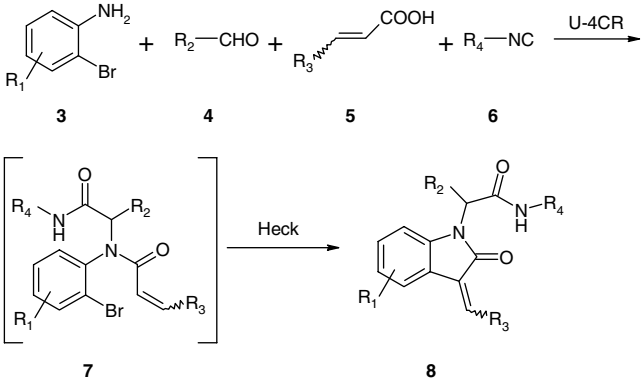
Abstract—A novel one-pot-synthesis of highly substituted indol-2-ones using a combination of Ugi and Heck reaction (U-4CR-Heck) is described. The synthesized indol-2-ones represent an interesting pharmacological scaffold with four potential points of diversity. Thus, this novel reaction-type is amenable to combinatorial high-throughput screening.

Compounds containing the indol-2-one scaffold constitute an important pharmacophoric moiety, which exhibits important biological effects such as antitumor activity (1),[1,2] phosphodiesterase inhibitor activity (2),[3] and tyrosine kinase inhibitor activity (3).[4–8] These examples illustrate the ongoing interest toward the scaffolds containing indol-2-ones (Fig. 1). However, the described synthetic strategies to indol-2-ones have found limitations mainly due to the lack of versatility and a limited number of appropriate initial reactants. In addition, they have not provided a robust method suitable for the production of combinatorial libraries.

Therefore we developed a novel one-pot synthesis of the indol-2-one core structure by combining combinatorial and classical sequential chemistry (Scheme 1). The presented novel Ugi–Heck reaction (U-4CR-Heck) describes an extension of former presented works. Therein Gracias et al.[9] and Yang et al.[10] developed independently from each other an Ugi/Heck two-step



Scheme 1. One-pot indol-2-one synthesis via U-4CR-Heck.

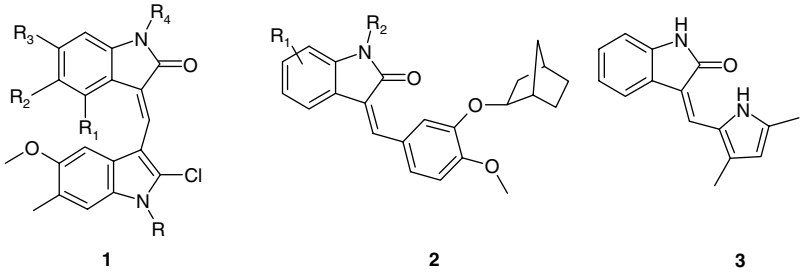


Figure 1. Pharmacological interesting structures incorporating the indol-2-one motif.

Keywords: Ugi reaction; Heck reaction; One-pot synthesis; Indol-2-ones; Multicomponent reaction; Combinatorial chemistry.
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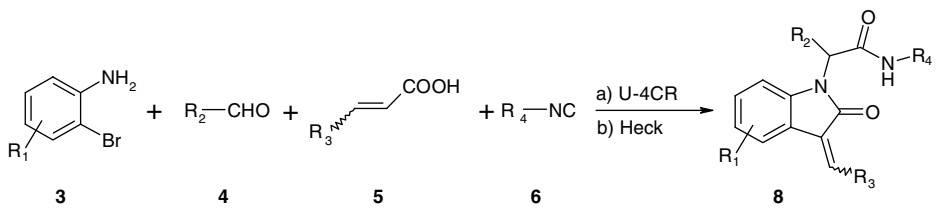
Table 1. Synthesized indol-2-ones



3 **4** **5** **6** **8**

Entry	R_1	R_2	R_3	R_4	Yield (%) (isomeric mixtures)	Product
1	H	C_6H_5	C_6H_5	CH_2–$COOCH_3$	59	**8a**
2	H	$CH(CH_3)_2$	C_6H_5	CH_2–$COOCH_3$	63	**8b**
3	H	H	C_6H_5	CH_2–$COOCH_3$	52	**8c**
4	H	C_6H_5	C_6H_5	$C(CH_3)_3$	54	**8d**
5	H	H	C_6H_5	CH_2–C_6H_5	48	**8e**
6	H	H	*p*-NO_2–C_6H_4	CH_2–$COOCH_3$	43	**8f**
7	H	H	*p*-NO_2–C_6H_4	CH_2–C_6H_5	58	**8g**
8	H	H	*m*-CF_3–C_6H_4	CH_2–$COOCH_3$	46	**8h**
9	H	C_6H_5	*m*-CF_3–C_6H_4	CH_2–$COOCH_3$	62	**8i**
10	H	H	*m*-*p*-MeO–C_6H_3	CH_2–$COOCH_3$	43	**8j**
11	H	H	*m*-*p*-MeO–C_6H_3	CH_2–C_6H_5	60	**8k**
12	H	H	CH_3	CH_2–$COOCH_3$	45	**8l**
13	NO_2	H	C_6H_5	$C(CH_3)_3$	35	**8m**

(a) Trifluorethanol; 24 h; 50 °C.
(b) Acetonitrile; 24 h; 80 °C; $Pd(OAc)_2$; PPh_3.

synthesis of N-heterocycles, using the advantages of multicomponent and classical sequential chemistry. The combination of multicomponent reactions and different post-reactions results in a maximum of diversity, which is well reported by different working groups.[11–17]

Multicomponent reactions like the Ugi reaction allow rapid generation of compound libraries[18–24] and the final intramolecular Heck reaction is used for a defined ring-closing. The obtained high substituted indol-2-ones have four points of potential diversity. Thus this novel reaction type is amenable to high-throughput combinatorial library production.

The formation of the acyclic products (**7**) was originally reported by Ugi et al. and the final ring-closing was performed by a classical intramolecular Heck reaction[25–29] (Scheme 1). These two reaction steps were combined in a new one-pot synthesis. The Ugi–Heck reaction was performed in a typical procedure,[30] whereby the starting materials were mixed in equimolar amounts and stirred for 24 h at 50 °C. Afterwards solvent was changed from polar protic to polar aprotic and 10% of Pd-catalyst were added. The reaction mixture was stirred for another 24 h at 80 °C. The expected compounds (**8a**–**m**) were isolated as isomeric mixtures with moderate to good yields (Table 1). Their assignment was made on the base of ^1H NMR, ^{13}C NMR, and HPLC–MS data. All the synthesized compounds have purity >95%.

In this letter we show an efficient synthesis of various types of 1,3-disubstituted indol-2-ones (Table 1). The used aldehydes, anilines, isocyanides, and acrylic acids can be varied broadly, producing products with four potential points of diversity.

In summary, a novel one-pot solution phase procedure for the preparation of indol-2-ones has been reported. With final products containing four points of potential diversity and a facile and rapid production protocol, access to thousands of diverse analogues with the aforementioned core structure is now feasible.

Current efforts are now focused on further extension of this novel reaction type.

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30. Typical procedure: The aldehyde (3 mmol) and the amine (3 mmol) were stirred in 5 ml trifluoroethanol for 1 h at room temperature. Then 3 mmol of acid and 3 mmol of isocyanide were added. The reaction mixture was stirred for 16 h at 50 °C until the reaction was completed (indication by TLC). After the reaction was completed, the solvent was evaporated and the resulting residue was dissolved in 5 ml of acetonitrile and 0.3 mmol $Pd(OAc)_2$ and 0.6 mmol PPh_3 were added. The reaction mixture was stirred for additional 16–24 h at 80 °C. Afterwards the solvent was evaporated again and the resulting residue was dissolved in ethyl acetate and filtered through a pad of silica. The resulting crude product was purified by crystallization from ethanol or by column chromatography on silica gel (hexane/ethyl acetate).
Compound **8c** was isolated in 52% yield as a yellow solid (mp 156 °C). ^{1}H NMR ($CDCl_3$, 250.13 MHz): 3.69 (s, 3H, CH_3), 4.03 (d, $^3J = 5.3$ Hz, 2H, CH_2), 4.49 (s, 2H, CH_2), 6.87 (s, 1H, N*H*), 6.90–7.66 (m, 9H, C_6H_5), 7.84 (s, 1H, C*H*=C). ^{13}C NMR ($CDCl_3$, 62.90 MHz): 41.1 (*C*H_2), 43.9 (*C*H_2), 52.3 (*C*H_3), 109.0, 121.1 (Cq), 122.5, 122.8, 126.3 (Cq), 128.6, 129.3, 130.0, 134.5 (Cq), 138.3 (*C*H=C), 142.5 (Cq), 167.5 (*C*ON), 168.7 (*C*ON), 169.8 (*C*OOCH$_3$). MS (ESI): $m/z = 351.1$ $[M+H]^+$, 373.2 $[M+Na]^+$.
Compound **8d** was isolated in 54% yield as a yellow-brown solid (mp 194 °C). ^{1}H NMR ($CDCl_3$, 250.13 MHz): 1.34 {s, 9H, C(CH_3)$_3$}, 6.27 (s, 1H, C*H*–C_6H_5), 6.80–7.53 (m, 14H), 7.59 (s, 1H, C*H*=C), 8.23 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 62.90 MHz): 28.5 {C(*C*H$_3$)$_3$}, 51.9 {*C*(CH$_3$)$_3$}, 58.9 (*C*H–C_6H_5), 111.8, 118.8, 122.0, 124.2, 125.3, 128.1, 128.2, 128.6, 128.7, 128.8, 130.5, 131.9, 133.7, 134.6, 137.7, 140.4, 166.3 (*C*ON), 167.1 (*C*ON). MS (ESI): $m/z = 411.0$ $[M+H]^+$, 433.3 $[M+Na]^+$.
Compound **8g** was isolated in 58% yield as a yellow solid (mp 251 °C). ^{1}H NMR (DMSO, 250.13 MHz): 4.32 (d, $^3J = 5.11$ Hz, 2H, CH_2), 4.49 (s, 2H, CH_2), 6.89–7.48 (m, 9H), 7.79 (s, 1H, C=C*H*), 8.00 (d, $^3J = 8.46$ Hz, 2H, –C_6H_4–NO_2), 8.37 (d, $^3J = 8.46$ Hz, 2H, –C_6H_4–NO_2), 8.77 (t, 1H, $^3J = 5.11$ Hz, –CH_2–N*H*–). ^{13}C NMR (DMSO, 62.90 MHz): 42.2 (*C*H_2), 42.5 (*C*H_2), 109.4, 119.8, 122.0, 123.2, 124.0, 126.8, 127.2, 128.3, 129.0, 130.5, 130.8, 132.5, 133.7, 139.1, 141.3, 144.1, 147.5, 165.2 (*C*ON), 166.5 (*C*ON), 167.0 (*C*ON). MS (ESI): $m/z = 414.5$ $[M+H]^+$, 436.5 $[M+Na]^+$.
Compound **8l** was isolated in 45% yield as a yellow oil. ^{1}H NMR ($CDCl_3$, 250.13 MHz): 1.94 (d, $^3J = 7.0$ Hz, 3H, CH_3–CH), 3.78 (s, 3H, COOCH_3), 4.10 (d, $^3J = 5.24$ Hz, 2H, CH_2), 4.67 (s, 2H, CH_2), 6.69 (s, 1H, N*H*), 6.87–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.90 MHz): 18.2 (*C*H_3), 40.8 (*C*H_2), 43.6 (*C*H_2), 52.5 (COO*C*H_3), 108.6, 119.1, 121.3, 122.7, 127.0, 128.8, 138.9, 147.2, 167.5 (*C*ON), 167.7 (*C*ON), 170.0 (*C*OOCH$_3$). MS (ESI): $m/z = 289.1$ $[M+H]^+$, 311.3 $[M+Na]^+$.