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Highly substituted indol-2-ones, quinoxalin-2-ones and benzodiazepin-2,5-diones via a new Ugi(4CR)-Pd assisted *N*-aryl amidation strategy

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Abstract—A new strategy employing an Ugi four-component reaction and a palladium-assisted intramolecular *N*-aryl amidation reaction is reported. The straight forward two-step synthesis generates *N*-heterocyclic compounds with four points of diversity from trivial starting materials with acceptable yields. This new reaction is also suitable for the generation of compound libraries.

Combinatorial chemistry has recently gained much attention in pharmaceutical research, especially in the context of lead finding and lead optimization.[1–3] Multicomponent reactions (MCRs) allow rapid generation of compound libraries containing a variety of different and highly relevant heterocyclic scaffolds.[4–10]

Therefore several research groups described new multicomponent reactions based on the combination of combinatorial and classical chemistry. By using appropriate starting materials in MCRs, a large range of classical post-condensation reactions are tolerated, yielding new interesting scaffolds.[11] The Ugi–Heck strategy reported at the same time by Gracias et al.[12] and Xiang et al.[13] offers a new potential for the Ugi reaction and very many scaffolds based on this strategy can still be envisioned.[14]

The area of palladium chemistry is diverse and a plethora of post-condensation modifications can be envisaged. Thus, we report herein a new strategy for the synthesis of highly substituted *N*-heterocyclic scaffolds based on the combination of the Ugi four-component reaction and a palladium-assisted intramolecular *N*-aryl amidation (Scheme 1).

The formation of the secondary amide **1** was originally reported by Ugi et al.[15] The final ring-closing reaction was performed by a classical intramolecular *N*-aryl amidation of secondary amides catalyzed by palladium and an appropriate ligand system under basic conditions. This reaction was extensively investigated and optimized by Buchwald and co-workers[16–19] who developed highly specific ligands to obtain high yields and short reaction times.

We started our investigation by combining these two reactions sequentially. Thus, the Ugi-reaction was performed in a typical procedure whereby amine, carbonyle, carboxylic acid and isocyanide were mixed in equimolar quantities in polar protic solvents (methanol, trifluoroethanol).[20] The Ugi-synthesis generally presented good to high yields and the purification of the desired secondary amide **1** was performed by crystallization or chromatographic methods. In the second step of our reaction sequence, the Ugi-product **1** was dissolved in toluene and the N-amidation was performed at 100 °C by using the catalytic system tris(dibenzylideneacetone) di-palladium $Pd_2(dba)_3$, tri-*o*-tolylphosphine as ligand and a carbonate base (caesium carbonate with the use of aliphatic isocyanides or potassium carbonate with the use of benzylic isocyanides according to the

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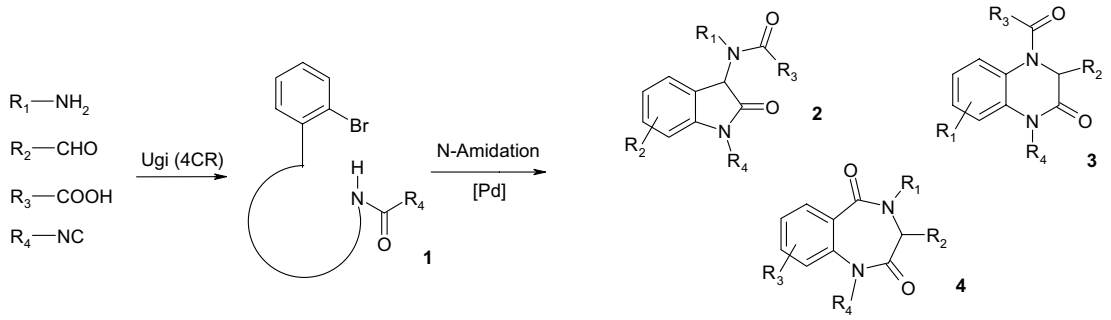


Scheme 1. General strategy.

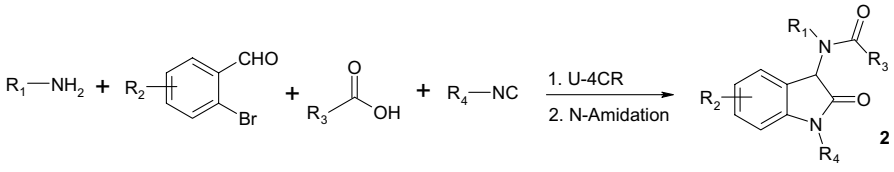
empiric observations).[21] The expected *N*-heterocyclic compounds were successfully isolated with moderate to good yields (Table 1). They were characterized by ^{1}H NMR, ^{13}C NMR and HPLC–MS data as well as elemental analyses. All the synthesized compounds had purities >95%.

With the use of substituted 2-bromobenzaldehydes, our synthetic strategy yields indol-2-ones **2** with four points of diversity. Table 1 shows the synthesized compounds with respective yields for each step (Y_1, Y_2).

The synthesized indol-2-ones are obtained with acceptable yields and aliphatic or benzylic isocyanides can be used successfully. Advantageously, the Ugi-reaction supports the use of functionalized 2-bromobenzaldehydes, which enables further construction on the scaffold (**2c**,**d**).

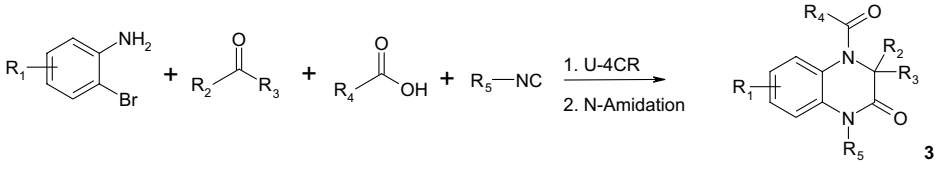
Following the same strategy, high substituted quinoxalin-2-ones **3** are obtained by the use of 2-bromoanilines (Table 2). Results prove that our strategy enables the preparation of the desired products with moderate to good yields. Both aldehydes and ketones could be employed in this reaction. Moreover, the Ugi-reaction supports the use of substituted or functionalized 2-bromoanilines (**1h**,**i**) but very electronic poor systems were not tolerated by the Ugi-reaction (**1j**).

Table 1. Synthesized indol-2-ones



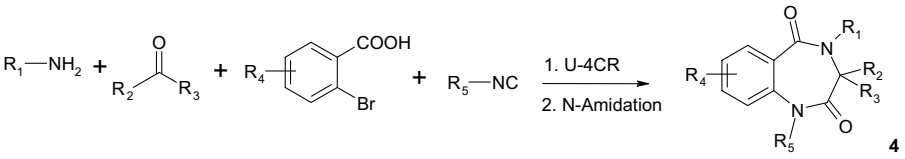
Entry	R_1	R_2	R_3	R_4	Y_1	Product	Y_2	Product
1	$CH–(CH_3)_2$	H	CH_3	C_2H_5	36	**1a**	25	**2a**
2	$CH–(CH_3)_2$	H	CH_3	$CH_2–C_6H_5$	42	**1b**[25]	25	**2b**[26]
3	$CH–(CH_3)_2$		CH_3	$CH_2–C_6H_5$	46	**1c**	45	**2c**
4	$CH–(CH_3)_2$	*m*-F	CH_3	$CH_2–C_6H_4–p$-OCH_3	53	**1d**	41	**2d**[27]
5	$CH_2–C_6H_5$	H	C_6H_5	$C–(CH_3)_3$	74	**1e**	4	**2e**

Table 2. Synthesized quinoxalin-2-ones



Entry	R_1	R_2	R_3	R_4	R_5	Y_1	Product	Y_2	Product
1	H	H	H	CH_3	CH_3	54	**1f**[28]	25	**3a**[29]
2	H	CH_3	CH_3	H		28	**1g**	37	**3b**
3	*p*-CH_3	H	H	CH_3	$CH_2–C_6H_5$	61	**1h**	45	**3c**
4	*p*-F	H	H	C_6H_5	CH_3	56	**1i**	50	**3d**[30]
5	*p*-$COOCH_3$	H	H	CH_3	$CH_2–C_6H_5$	0	**1j**	1–3	—

Table 3. Synthesized benzodiazepin-2,5-diones



4

Entry	R_1	R_2	R_3	R_4	R_5	Y_1	Product	Y_2	Product
1		H	H	H	CH_3	87	**1k**	28	**4a**[31]
2	CH_2–C_6H_5	CH_3	CH_3	H	CH_3	59	**1l**	32	**4b**
3	CH–$(CH_3)_2$	H	H	H	CH_2–CH_3	57	**1m**	33	**4c**
4	$(CH_2)_2$–O–CH_3	CH_2–CH_3	H	H	CH_2–C_6H_4–*p*-OCH_3	25	**1n**	51	**4d**

Finally, we improved the synthesis of substituted benzodiazepin-2,5-diones **4** by involving 2-bromobenzoic acids derivates in the Ugi-*N*-aryl amidation reaction. This strategy represents an alternative for the synthesis of this scaffold which can also be obtained by other synthetic routes[22–24] based on multi-component chemistry.

Table 3 shows different benzodiazepine-2,5-diones **4a–d** synthesized via U(4CR)-*N*-aryl amidation reaction with specific yields. Once more, aliphatic and benzylic isocyanides as well as aldehydes or ketones could be involved with success.

In summary, a novel two-step solution phase procedure for the preparation of indol-2-ones, quinoxalin-2-ones and benzodiazepine-2,5-diones has been reported. With final products containing four points of potential diversity and a facile and rapid production protocol, access to thousands of compounds containing the outlined important pharmacophoric scaffolds is now feasible.

Current efforts are now focussing on the investigation of the scope and limitations of this reaction-type and the development of a one-pot procedure based on this strategy.

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20. General procedure (GP1) for the synthesis of the Ugi-products **1a–n**: aldehyde (3 mmol) and 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 24–72 h at room temperature (or at 50 °C when using paraformaldehyde). Then, the solvent was evaporated and the crude product was purified by crystallization or chromatographic methods.
21. General Procedure (GP2) for the intramolecular palladium-catalyzed aryl amination of secondary amides: the Ugi-product **1** (1 mmol) was solved in 3 mL dry toluene. $Pd_2(dba)_3$ (0.05 mmol), tri-*o*-tolylphosphine (0.1 mmol) and 2 mmol of the base (Cs_2CO_3 for aliphatic isocyanides or K_2CO_3 for benzylic isocyanides) were added and the mixture was stirred at 100 °C for 72–96 h. Then, 20 mL methylene chloride was added, the mixture was filtered and the organic layer was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the crude product was purified by crystallization or chromatographic methods.
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25. Compound **1b** was prepared according to GP1 and purified by chromatography on silica gel with ethyl acetate as eluent to afford a white solid. ^1H ($CDCl_3$, 250.13 MHz): 0.90 (d, 3H, $^3J = 6.64$ Hz, N–CH–(CH_3)$_2$), 1.46 (d, 3H, $^3J = 6.64$ Hz, N–CH–(CH_3)$_2$), 2.27 (s, 3H, CH_3–C=O), 4.14 (m, 1H, N–CH–$(CH_3)_2$), 4.45 (dd, 2H, $^2J = 17.37$ Hz, $^3J = 5.84$ Hz, NH–CH_2–Ph), 5.19 (s, 1H, CH–C_6H_4–Br), 5.51 (m, 1H, NH), 7.16–7.32 (m, 7H, ar-H); 7.54–7.64 (m, 2H, ar-H). ^{13}C ($CDCl_3$, 62.89 MHz): 20.60 (N–CH–(CH_3)$_2$), 21.36 (N–CH–(CH_3)$_2$), 22.48 (CH_3–C=O), 43.77 (NH–CH_2–Ph), 50.76 (N–CH–$(CH_3)_2$), 60.99 (*C*H–Ph–Br), 124.41, 127.04, 127.39, 128.40, 129.94, 130.48, 133.09, 136.47. 138.11 (ar), 168.19 (O=*C*–NH), 170.97 (CH_3–*C*=O). MS (ESI): $m/z = 405$ $[M+H]^{+\cdot}$.

26. Compound **2b** was prepared from **1b** according to GP2 and purified by chromatography on silica gel with the eluent ethyl acetate to afford a light beige solid. ^{1}H ($CDCl_3$, 250.13 MHz): 1.47 (d, 6H, $^3J = 6.64$ Hz, N–CH–(CH_3)$_2$), 2.13 (s, 3H, CH_3–C=O), 4.25 (h, $^3J = 6.64$ Hz, N–CH–(CH_3)$_2$), 4.50 (s, 1H, CH–N–C(O)–CH_3), 4.96 (s, 2H, CH_2–Ph), 6.64 (d, 1H, $^3J = 7.59$ Hz, ar-H), 6.95–6.98 (m, 1H, ar-H), 7.09 (d, $^3J = 7.43$ Hz, ar-H), 7.22–7.31 (m, 5H, ar-H). ^{13}C ($CDCl_3$, 62.89 MHz): 21.67 (N–CH–(CH_3)$_2$), 21.78 (N–CH–(CH_3)$_2$), 22.83 (CH_3–C=O), 44.12 (CH_2-Ph), 49.45 (N–CH–(CH_3)$_2$), 54.74 (CH–N–C(O)–CH_3), 109.20, 122.17, 122.25, 126.43, 127.20, 127.32, 128.34, 128.70, 136.00, 143.33 (ar), 168.80 CH-C(N)=O), 174.28 (CH_3–C=O). MS (ESI): $m/z = 323$ [M+H]$^+$, 345 [M+Na]$^+$.
27. Compound **2d** was prepared from **1d** according to GP2 and purified by chromatography on silica gel with the system ethyl acetate–hexane 9:1 to afford a white solid. ^{1}H ($CDCl_3$, 215.13 MHz): 1.45 (d, 3H, $^3J = 6.55$ Hz, CH–(CH_3)$_2$), 1.47 (d, 3H, $^3J = 6.55$ Hz, CH–(CH_3)$_2$), 2.14 (s, 3H, CH_3–C=O), 3.76 (s, 3H, C_6H_4–O–CH_3), 4.25 (h, 1H, $^3J = 6.55$ Hz, CH–(CH_3)$_2$, 4.81 (d, 1H, $^2J = 15.8$ Hz, CH_2–C_6H_4), 4.96 (d, 1H, $^2J = 15.8$ Hz, CH_2–C_6H_4), 6.52–6.57 (m, 1H, ar-H), 6.71–6.87 (m, 4H, ar-H), 7.31 (d, $^3J = 8.53$ Hz, ar-H). ^{13}C ($CDCl_3$, 62.89 MHz): 21.58 (N–CH–(CH_3)$_2$), 21.72 (N–CH–(CH_3)$_2$), 22.81 (CH_3–C=O), 43.69 (CH_2–Ph), 49.44 (N–CH–(CH_3)$_2$), 54.83 (CH–N–C(O)–CH_3), 55.20 (O–CH_3), 109.66, 110.20, 110.60, 114.15, 114.26, 114.52, 127.62, 128.03, 128.15, 128.49, 139,18 (ar), 158.94 (C–O–CH_3), 159.07 (d, $^1J_{(C-F)} = 239.91$, C–F), 168.80 (CH–C(N)=O), 174.28 (CH_3–C=O). MS (ESI): $m/z = 371$ [M+H]$^+$, 393 [M+Na]$^+$.
28. Compound **1f** was prepared according to GP1 and purified by crystallization from ethyl acetate-hexane to afford a white solid. ^{1}H ($CDCl_3$, 250.13 MHz): 1.87 (s, 3H, CH_3–C=O), 2.83 (d, 3H, $^3J = 4.81$ Hz, CH_3–NH–C=O), 3.70 (d, 1H, $^2J = 15.09$ Hz, N–CH_2–C=O), 4.67 (d, 1H, $^2J = 15.09$ Hz, N–CH_2–C=O), 6.52 (m, 1H, NH), 7.22–7.30 (m, 1H, ar-H), 7.35–7.43 (m, 1H, ar-H), 7.67 (dd, 1H, $^3J = 7.83$ Hz, $^4J = 1.13$ Hz, ar-H). MS (ESI): $m/z = 286$ [M+H]$^+$, 308 [M+Na]$^+$.
29. Compound **3a** was prepared from **1f** according to GP2 and purified by crystallization from ethanol to afford a beige solid. ^{1}H ($CDCl_3$, 200.04 MHz): 2.26 (s, 3H, CH_3–C=O), 3.37 (s, 3H, N–CH_3), 4.50 (s, 2H, O=C–CH_2–N), 7.08–7.17 (m, 2H, ar-H); 7.29–7.33 (m, 2H, ar-H). ^{13}C ($CDCl_3$, 62.89 MHz): 21.87 (CH_3–C=O); 29.00 (N–CH_3), 45.89 (N–CH_2–C=O), 115.46, 122.96, 124.02, 126.67, 128.51, 134.26 (ar), 167.3 (CH_3–C=O), 168.91 (N–CH_2–C=O). MS (ESI): $m/z = 286$ [M+H]$^+$, 308 [M+Na]$^+$.
30. Compound **3d** was prepared from **1i** according to GP2 and purified by chromatography on silica gel with the eluent ethyl acetate to afford a beige solid. ^{1}H ($CDCl_3$, 250.13 MHz): 3.38 (s, 3H, N–CH_3), 4.53 (s, 2H, N–CH_2–C=O), 6.51–6.58 (m, 1H, ar-H), 6.80 (dd, 2H, $^3J = 9.79$ Hz, $^4J = 2.69$ Hz, ar-H), 7.28–7.35 (m, 5H, ar-H). ^{13}C ($CDCl_3$, 62.89 MHz): 29.39 (N–CH_3), 48.51 (N–CH_2–C=O), 103.02, 103.46, 109.31, 125.89, 126.04, 128.50, 128.74, 131.22, 133.77, 134.75, 134.91 (ar), 160.56 (d, $^1J_{(C-F)} = 245.43$ Hz, C–F), 166.57 (CH_3–C=O), 168.91 (N–CH_2–C=O). MS (ESI): $m/z = 285$ [M+H]$^+$, 307 [M+Na]$^+$. Anal. Calcd for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.39; H, 4.63; N, 9.53.
31. Compound **4a** was prepared from **1k** according to GP2 and purified by chromatography on silica gel with the eluent ethyl acetate to afford a white solid. ^{1}H ($CDCl_3$, 250.13 MHz): 1.25 (s, 4H, CH_2 cyclopropyl), 2.04 (m, 1H, CH cyclopropyl), 2.84 (s, 3H, N–CH_3), 4.32 (s, 2H, O=C–CH_2–N), 7.10 (d, 1H, $^3J = 7.42$ Hz, ar-H), 7.33 (dd, 1H, $^3J = 7.58$ Hz, $^4J = 1.26$ Hz, ar-H), 7.42 (dt, 1H, $^3J_a = 7.42$ Hz, $^3J_b = 7.58$ Hz, ar-H), 7.85 (dd, 1H, $^3J = 7.58$ Hz, $^4J = 1.42$ Hz, ar-H). ^{13}C ($CDCl_3$, 62.89 MHz): 26.32 (CH_2 cyclopropyl), 29.7 (CH_2 cyclopropyl), 31.3 (N–CH_3), 52.97 (O=C–CH_2–N); 119.21, 126.58, 129.78, 131.22, 132.93, 143.38 (ar), 168.95 (O=C–CH_2), 169.88 (O=C–N-cyclopropyl). MS (ESI): $m/z = 253$ [M+Na]$^+$.