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One-pot synthesis of quinolin-2-(1*H*)-ones via tandem Ugi–Knoevenagel condensations ☆

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Abstract—A new application of the Ugi reaction in the synthesis of heterocyclic compounds is described. Substituted quinolin-2-(1*H*)-ones are formed in one-pot sequential Ugi four-component condensation and intramolecular Knoevenagel cyclization between *o*-acylanilines, aldehydes, malonic or tosylacetic acids and cyclohexyl isocyanide.

3-Substituted quinolin-2(1*H*)-ones bearing electron withdrawing groups have attracted considerable attention because of their pharmacological properties. These structures are present in several glycine NMDA receptor antagonists,[1] endothelin receptor antagonists[2] and farnesyl transferase inhibitors.[3] Some quinolin-2(1*H*)-ones have been used as intermediates in the synthesis of HIV-1 reverse transcriptase inhibitors,[4] 5-HT_3 receptor antagonists[5] or AMPA/kainate antagonists.[6] The growing importance of these pharmaceutical compounds has led to the development of new methods for their synthesis, including those performed on solid phase[7] or under microwave irradiation in solvent-free conditions.[8] Moreover, peptidomimetic inhibitors of proteases, containing aromatic heterocycles, are emerging as potential therapeutic agents.[9] Heterocycles confer conformational rigidity and improve physical properties, such as charge density or lipophilicity, and pharmacological advantages, such as metabolic stability and oral bioavailability. In continuation of our studies on the synthesis of heterocyclic compounds from isocyanides,[10] we have developed a convenient method for the preparation of quinolinones by means of a tandem Ugi four-component/Knoevenagel condensations.

The reaction sequence is illustrated in Scheme 1. The 2-aminophenylketones (**1a**–**b**) were treated with aldehydes (**2a**–**e**), cyclohexylisocyanide (**3**) and malonic or arylsulfonylacetic acid derivatives (**4a**–**d**) to form the corresponding bisamides **5a**–**k** that underwent an intramolecular Knoevenagel reaction between the reactive methylene and the carbonyl group. This general methodology allowed convenient synthesis of substituted quinolinones. The influence of the electron withdrawing group was examined by the use of different malonic or arylsulfonylacetic acid derivatives. When R^3 was a cyano or a carboxylate group, the Knoevenagel reaction was spontaneously performed in the initial acidic conditions used for the Ugi reaction. But when R^3 was an arylsulfonyl group the reaction stopped after the Ugi reaction and products **5i**–**k** could be isolated. In these cases the cyclization to the quinolinone was achieved by adding a base.

In a typical experiment, a solution of cyclohexylisocyanide (**3**) (1 mmol) in methanol (4 mL) was added to a solution of aminoketone **1a**–**b** (1 mmol), aldehyde **2a**–**e** (1 mmol) and malonic (**4a**–**b**) or arylsulfonylacetic acid (**4c**–**d**) derivative (1 mmol) in methanol (4 mL). The resulting mixture was stirred for 48 h for **6a**–**f** and **5i**–**k**, and 96 h for **6g**–**h** at room temperature and then filtered to give **6a**–**h** (51–78%) or **5i**–**k** (58–74%). Knoevenagel condensation of bisamides **5i**–**k** was achieved by treating a solution of **5i**–**k** (1 mmol) in methanol (5 mL) with NaH (96 mg, 4 mmol). The resulting suspension was stirred for 4 h at room temperature, evaporated to dryness and the residue stirred with H_2O (8 mL) and filtered

Keywords: Ugi reaction; Knoevenagel condensation; Quinolinone.
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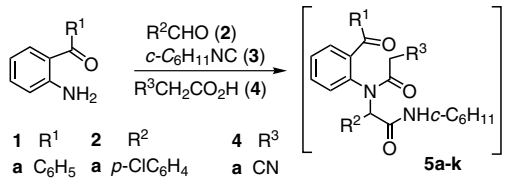
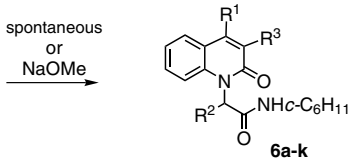


1	R^1	2	R^2	4	R^3
a	C_6H_5	a	*p*-ClC_6H_4	a	CN
b	CH_3	b	C_6H_5	b	$CO_2CH_2CH_3$
		c	*p*-$CH_3OC_6H_4$	c	$SO_2C_6H_4$-*p*-CH_3
		d	C_6H_5CH=CH	d	$SO_2C_6H_4$-*p*-NHCOCH$_3$
		e	*p*-$CH_3C_6H_4$		



5, 6	R^1	R^2	R^3	6(%)
a	C_6H_5	*p*-ClC_6H_4	CN	(56)
b	C_6H_5	C_6H_5	CN	(51)
c	C_6H_5	*p*-$CH_3OC_6H_4$	CN	(69)
d	C_6H_5	C_6H_5CH=CH	CN	(78)
e	CH_3	*p*-ClC_6H_4	CN	(63)
f	CH_3	*p*-$CH_3C_6H_4$	CN	(72)
g	C_6H_5	*p*-ClC_6H_4	CO_2Et	(62)
h	C_6H_5	*p*-$CH_3C_6H_4$	CO_2Et	(67)
i	C_6H_5	*p*-ClC_6H_4	$SO_2C_6H_4$-*p*-CH_3	(63)
j	C_6H_5	*p*-$CH_3C_6H_4$	$SO_2C_6H_4$-*p*-CH_3	(72)
k	C_6H_5	*p*-ClC_6H_4	$SO_2C_6H_4$-*p*-NHCOCH$_3$	(58)

Scheme 1. Quinolin-2-(1*H*)-ones via tandem Ugi–Knoevenagel condensations.

to give **6i**–**k**, in good yieds (92–95%). Using a similar procedure **6i**–**k** were obtained in one pot from cyclohexylisocyanide (**3**), aminoketone **1a**, aldehyde **2a**,**e** and arylsulfonylacetic acid derivative **4c**–**d**, by stirring the resulting mixture in methanol for 48 h at room temperature and then treating the reaction mixture with sodium methoxide (from NaH, 96 mg, 4 mmol) and stirring for 4 h at room temperature. Similar work-up of previous reactions gave **6i**–**k** in comparable yields (58–72%).

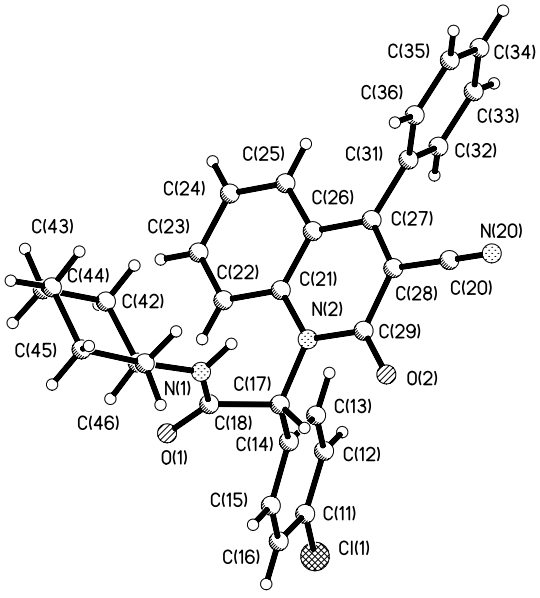


Figure 1. The molecular structure of **6a**.

The structure of **6a** was confirmed by single crystal X-ray diffraction (Fig. 1). Crystal and refinement data are summarized in Ref. 11.

In summary, we have developed a facile and selective synthesis of substituted quinolin-2(1*H*)-ones by a one-pot Ugi four component reaction followed by an intramolecular Knoevenagel condensation, starting from commercial or easily prepared reagents.

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11. All new compounds gave satisfactory spectral and elemental analysis (selected examples are given).

2-(3-Cyano-2-oxo-4-phenyl-2H-quinolin-1-yl)-N-cyclohexyl-2-(4′-chlorophenyl)acetamide (**6a**): Pale yellow solid, 56%, mp 214–216 °C. IR (KBr, cm^{-1}) ν 2237 (CN), 1689 (CO), 1658 (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98–1.34 (m, 5H), 1.53–1.70 (m, 4H), 1.93–1.96 (m, 1H), 3.71–3.83 (m, 1H), 6.34 (d, $J = 6.3$, 1H, NH), 6.92 (br s, 1H), 7.08–7.56 (m, 13H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 24.9, 25.0, 25.6, 32.7, 32.8 (5×CH_2) 49.4, 60.8 (2×CH), 115.0 (Cq), 117.9 (CH_{Ar}), 120.4 (Cq), 123.8, 129.0, 129.1, 129.2, 129.3, 129.5, 130.1, 130.5 (11×CH_{Ar}), 132.4, 133.6 (3×Cq), 133.7 (CH_{Ar}), 134.5, 140.0, 159.8, 160.9, 166.1 (5Cq). MS (EI, *m/z*, %) 495 (M^+, 6), 398 (37), 396 (100). HRMS $M^+_{found} = 495.1721$, $C_{30}H_{26}ClN_3O_2$ requires 495.1714. Anal. Calcd for $C_{30}H_{26}ClN_3O_2$: C, 72.65; H, 5.28; N, 8.47. Found: C, 72.41; H, 5.31; N, 8.68.

Crystal data for **6a**: $C_{30}H_{26}ClN_3O_2$, $M_r = 495.99$, monoclinic, space group $P2(1)/c$, $a = 14.925(9)$, $b = 16.559(10)$, $c = 10.687(6)$ Å, $\beta = 103.92(1)°$, $V = 2564(3)$ Å^3, $Z = 4$, $D_x = 1.285$ Mg m^{-3}, MoKα radiation (graphite crystal monochromator, $\lambda = 0.71073$), $\mu = 0.181$ mm^{-1}, $F(000) = 1040$, $T = 293(2)$. Final conventional $R = 0.0807$ and $w_2 = 0.1952$ for 5548 independent reflections (3719 observed with $I > 2\sigma(I)$) and 329 variables. CCDC 234701 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336-033; or deposit@ccdc.cam.ac.uk).

2-(3-Cyano-2-oxo-4-phenyl-2H-quinolin-1-yl)-N-cyclohexyl-4-phenyl-3-butenamide (**6d**): Pale yellow solid, 78%, mp 233–235 °C. IR (KBr, cm^{-1}) ν 2233 (CN), 1682 (CO), 1658 (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98–1.38 (m, 5H), 1.52–1.83 (m, 4H), 1.94–1.98 (m, 1H), 3.73–3.88 (m, 1H), 6.34 (d, $J = 7.7$, 1H, NH), 6.68 (d, $J = 16.2$, 1H), 6.93 (dd, $J = 16.2$, $J = 6.5$, 1H), 7.16–7.64 (m, 15H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 25.0, 25.2, 25.6, 32.9, 33.0 (5×CH_2), 49.3, 58.9 (2×CH), 115.1 (Cq), 117.2 (CH), 120.4 (Cq), 121.4, 123.7 (2×CH), 127.0, 128.8, 128.9, 129.0, 129.1, 130.3, 130.4 (10×CH_{Ar}), 133.6 (2×Cq), 133.9 (CH_{Ar}), 135.8 (Cq), 136.8 (CH_{Ar}), 139.6, 159.4, 160.6, 166.9 (4×Cq). MS (EI, *m/z*, %) 487 (M^+, 8), 396 (84), 388 (100). HRMS $M^+_{found} = 487.2264$, $C_{32}H_{29}N_3O_2$ requires 487.2260. Anal. Calcd for $C_{32}H_{29}N_3O_2$: C, 78.83; H, 5.99; N, 8.62. Found: C, 78.59; H, 5.98; N, 8.85.

*2-(3-Cyano-4-methyl-2-oxo-2H-quinolin-1-yl)-N-cyclohexyl-2-(4′-chlorophenyl)*acetamide (**6e**): White solid, 63%, mp 230–232 °C. IR (KBr, cm^{-1}) ν 2208 (CN), 1686 (CO), 1655 (CO). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95–1.39 (m, 5H), 1.54–1.79 (m, 4H), 1.92–1.94 (m, 1H), 2.83 (s, 3H), 3.64–3.84 (m, 1H), 6.10 (d, $J = 8.0$, 1H, NH), 6.85 (br s, 1H), 7.22–7.50 (m, 7H, H_{Ar}), 7.81–7.85 (m, 1H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 18.9 (CH_3), 24.9, 25.0, 25.6, 32.8, 32.9 (5×CH_2) 49.2, 60.2 (2×CH), 115.0 (Cq), 118.1 (CH_{Ar}), 120.4 (Cq), 124.0, 126.9, 129.2, 129.3, 129.5 (7×CH_{Ar}), 132.4 (Cq), 133.6 (CH_{Ar}), 134.4, 139.2, 158.0, 159.6, 166.1 (5×Cq). MS (EI, *m/z*, %) 433 (M^+, 10), 334 (100), 308 (73). HRMS $M^+_{found} = 433.1561$, $C_{25}H_{24}ClN_3O_2$ requires 433.1557. Anal. Calcd for $C_{25}H_{24}ClN_3O_2$: C, 69.20; H, 5.57; N, 9.68. Found: C, 69.01; H, 5.48; N, 9.53.

2-(3-Ethoxycarbonyl-2-oxo-4-phenyl-2H-quinolin-1-yl)-N-cyclohexyl-2-(4′-chlorophenyl)acetamide (**6g**): White solid, 62%, mp 192–193 °C. IR (KBr, cm^{-1}) ν 1732 (CO), 1687 (CO), 1633 (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.93 (t, $J = 7.0$, 3H), 0.94–1.40 (m, 5H), 1.51–1.79 (m, 4H), 1.92–2.02 (m, 1H), 3.72–3.89 (m, 1H), 4.06 (q, $J = 7.0$, 2H), 6.08 (d, $J = 8.1$, 1H, NH), 7.02–7.13 (m, 2H), 7.31–7.52 (m, 12H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 400 MHz) 13.6 (CH_3), 24.5, 24.6, 25.2, 32.4, 32.6, (5×CH_2), 48.8, 59.1 (2×CH), 61.3 (CH_2), 117.3 (CH_{Ar}), 120.7 (Cq), 122.9, 128.3, 128.6, 128.7, 128.9, 129.1, 131.1, 132.2 (10×CH_{Ar}), 133.5 (Cq), 134.1 (CH_{Ar}), 138.6, 149.4, 159.5, 165.1, 166.2 (5×Cq). MS (EI, *m/z*, %) 542 (M^+, 13), 443 (100). HRMS $M^+_{found} = 542.1974$, $C_{32}H_{31}ClN_2O_4$ requires 542.1972. Anal. Calcd for $C_{32}H_{31}ClN_2O_4$: C, 70.77; H, 5.75; N, 5.16. Found: C, 70.71; H, 5.62; N, 5.00.

2-(4-Chlorophenyl)-N-cyclohexyl-2-[2-oxo-4-phenyl-3-tosyl-2H-quinolin-1-yl]-acetamide (**6i**): Pale yellow solid, 63% (95% from **5i**), mp 155–157 °C. IR (KBr, cm^{-1}) ν 1682 (CO), 1656 (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85–1.33 (m, 5H), 1.53–1.68 (m, 4H), 1.78–1.85 (m, 1H), 2.39 (s, 3H), 3.59–3.70 (m, 1H), 5.98 (d, $J = 8.8$, 1H, NH), 6.70 (br s, 1H), 7.05–7.84 (m, 17H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 21.9 (CH_3), 24.8, 25.6, 32.5, 32.6 (5×CH_2), 49.0, 60.6 (2×CH), 117.0 (CH_{Ar}), 121.8 (Cq), 123.4, 128.2, 128.3, 128.8, 129.0, 129.1, 129.3, 130.9 (15×CH_{Ar}), 132.4 (Cq), 133.2 (CH_{Ar}), 134.2, 134.3, 138.5, 140.0, 144.1, 156.1, 158.4, 166.2 (9×Cq). MS (EI, *m/z*, %) 624 (M^+, 0.02), 84 (100). HRMS $M^+_{found} = 624.1829$, $C_{36}H_{33}ClN_2O_4S$ requires 624.1850. Anal. Calcd for $C_{36}H_{33}ClN_2O_4S$: C, 69.16; H, 5.32; N, 4.48; S, 5.13. Found: C, 68.93; H, 5.28; N, 4.44; S, 4.99.

2-[(2-Benzoylphenyl)-(2-tosylacetylamino)]-2-(4-chlorophenyl)-N-cyclohexylacetamide (**5i**): White solid, 65%, mp 166–168 °C. IR (KBr, cm^{-1}) ν 1693 (CO),1670 (CO), 1650 (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05–1.49 (m, 5H), 1.61–1.96 (m, 4H), 2.08–2.17 (m, 1H), 2.45 (s, 3H), 3.79–3.83 (m, 1H), 4.02 (d, $J = 14.4$, 1H), 4.31 (d, $J = 14.4$, 1H), 6.24 (s, 1H), 6.72 (s, 3H, H_{Ar}), 6.75–7.99 (m, 14H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 22.0 (CH_3), 25.3, 25.4, 25.7, 32.9, 33.3 (5×CH_2), 49.5 (CH), 61.9 (CH_2), 63.0 (CH), 128.3, 128.6, 128.7, 128.8, 129.9, 130.4, 131.1, 131.8, 131.9, 132.7, 132.9, 133.0, 133.5 (17×CH_{Ar}), 134.7, 135.6, 136.2, 136.7, 138.1, 145.3, 164.1, 167.8, 194.0 (10×Cq). MS (FAB, *m/z*, %) 643 (M^++1, 100), 544 (54), 460 (61). HRMS (FAB) $M^+_{found} = 643.2046$, $C_{36}H_{35}ClN_2O_5S$ requires 643.2033. Anal. Calcd for $C_{36}H_{35}ClN_2O_5S$: C, 67.23; H, 5.48; N, 4.35; S, 4.98. Found: C, 67.28; H, 5.29; N, 4.66; S, 5.11.