Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 90–93

Rearrangement of furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-diones to furo[3,4-*c*]quinoline-3,4(1*H*,5*H*)-diones

Stanislav Kafka,[a,*] Janez Košmrlj,[b,*] Antonín Klásek[a] and Andrej Pevec[b]

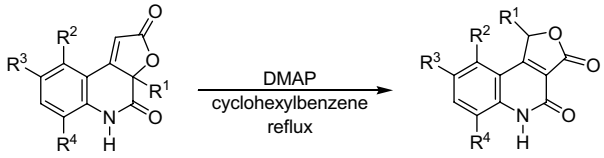
[a]*Faculty of Technology, Tomas Bata University in Zlín, 762 72 Zlín, Czech Republic*
[b]*Faculty of Chemistry and Chemical Technology, University of Ljubljana, 1000 Ljubljana, Slovenia*

Received 2 October 2007; revised 23 October 2007; accepted 1 November 2007
Available online 6 November 2007

Abstract—Thermally assisted base-catalyzed rearrangement of furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-diones **1** to the corresponding furo[3,4-*c*]quinoline-3,4(1*H*,5*H*)-diones **2** is reported, and a mechanism of the transformation is proposed.

In recent years, we have explored the reactivity of quinoline-2,4(1*H*,3*H*)-diones, and these studies have led to a number of interesting products.[1–3] For example, Wittig reaction of 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones with ethyl (triphenylphosphoranylidene)acetate ($Ph_3P=CHCO_2Et$) afforded the desired and expected (2*E*)-(3-hydroxy-2-oxo-2,3-dihydroquinolin-4(1*H*)-yl-idene)acetates.[1k] In some cases, furo[3,4-*c*]quinoline-3,4(1*H*,5*H*)-diones were also formed and isolated as by-products.[2] The formation of these compounds was tentatively explained through the rearrangement of intermediately formed furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-diones by the basic Wittig reagent ($Ph_3P=CHCO_2Et$) or triphenylphosphine. *Inter alia* we were intrigued by this rearrangement and decided to study it in more detail, and report our preliminary results in this Letter.

Starting furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-diones **1**, required to study the rearrangement shown in Scheme 1, were prepared by known chemistry from 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones.[2–4] To test whether the base catalyst was essential for the rearrangement, we initially conducted experiments with lactones **1a**,**d**–**f** in boiling cyclohexylbenzene without any additives. No reaction (data not shown) took place, and after 3 h of heating, the starting materials were nearly quantitatively recovered. As shown in Table 1, the addition of



1 **2**

Scheme 1.

4-dimethylaminopyridine (DMAP, 20 mol %) afforded the desired products in good yields.

In a general reaction procedure, a mixture of compound **1** (0.5 mmol) and DMAP (20 mol %) in cyclohexylbenzene (2 mL) was heated at reflux (~239 °C) under an inert atmosphere for 25–120 min. After cooling, the precipitated compound **2** was filtered under vacuum and recrystallized from the solvent indicated in Table 1. The yields of analytically pure products, obtained after the recrystallization, are given in Table 1. Careful monitoring of the reaction progress was found to be crucial as additional heating of the reaction mixture, after starting lactone **1** had been consumed, decreased the yield of **2**. The reaction times and the yields reported in Table 1 refer to the optimal reaction conditions. It is interesting to note that, in comparison to **1a**–**g**, compound **1h** was the most reactive. Conducting the reaction at 190–205 °C (Table 1, entry 9, conditions C) resulted in complete consumption of **1h** in 4 min, affording **2h** in 52% yield. If conditions A were applied, no **2h** could be detected in the reaction mixture, probable due to its fast decomposition.

Keywords: Rearrangement; Quinolones; Isocyanate; Mechanism.
* Corresponding authors. E-mail addresses: kafka@ft.utb.cz; janez.kosmrlj@fkkt.uni-lj.si

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.010

Table 1. Rearrangement of lactones **1** to furo[3,4-*c*]quinoline-3,4(1*H*,5*H*)-diones **2**[a]

Entry	1	R^1	R^2	R^3	R^4	Conditions	Time (min)	Yield[b] (%)	2, mp (°C, solvent)
1	**1a**	*n*-Bu	H	H	H	A	120	60	**2a**, 228–232 (EtOH)
2	**1b**	*n*-Bu	H	H	Me	A	90	41	**2b**, 229–236 (*n*-BuOH)
3	**1c**	*n*-Bu	H	Me	H	A	50	46	**2c**, 273–278 (EtOH)
4	**1c**	*n*-Bu	H	Me	H	B	100	44	**2c**
5	**1d**	Bn	H	H	H	A	25	53	**2d**, 289–294 (EtOH)
6	**1e**	Bn	Me	H	Me	A	40	64	**2e**, 288–292 (HOAc)[c]
7	**1f**	Bn	Cl	H	Me	A	40	66	**2f**, 281–283 (HOAc)[d]
8	**1g**	Ph	H	H	H	A	40	47	**2g**, 297–307 (DMF/EtOH)
9	**1h**	Ph	Me	H	Me	C	4	52	**2h**, 335–342 (DMF/EtOH)

[a] Conditions: (A) DMAP (20 mol %), cyclohexylbenzene (bp 239 °C), reflux; (B) $PhCH_2NH_2$ (2.2 equiv), cyclohexylbenzene, reflux; (C) DMAP (20 mol %), cyclohexylbenzene, bath temperature 190–205 °C.
[b] Refers to isolated, recrystallized products.
[c] Lit.[2] mp 282–285 °C (HOAc).
[d] Lit.[2] mp 280–284 °C (HOAc).

Confirmation of the structures of furo[3,4-*c*]quinoline-3,4(1*H*,5*H*)-diones **2** was provided by IR, MS, and NMR spectra, and in some cases 2D NMR spectra.[4] Proton H-1 and carbon C-1 resonances appeared at δ 5.87–6.94 ppm and δ 78.2–81.7, respectively, and were characteristic for compounds **2**. Single crystal X-ray structure determination corroborated the structure of **2b** (Fig. 1).[5] In the crystal, four molecules of **2b** are assembled into a framework by weak N5–H···O=C3 hydrogen bonds, as shown in Figure 2.

A mechanistic rationalization for the rearrangement is given in Scheme 2. Base-assisted deprotonation leads to intermediate resonance stabilized carbanion and isocyanate group, which after re-combination and subsequent enolization results in the formation of **2**. A similar isocyanate mechanism has been proposed for the rearrangement of 4-imino-(1*H*,4*H*)-3,1-benzoxazine-2-ones into 2,4-quinazolinediones by Azizian et al.[6] The authors trapped the isocyanate group with methanol leading to the corresponding methyl carbamate. In accordance with the proposed mechanism, the authors also reported that the *N*-methyl derivative which cannot form an isocyanate did not rearrange. Our proposed mechanism is in agreement with the fact

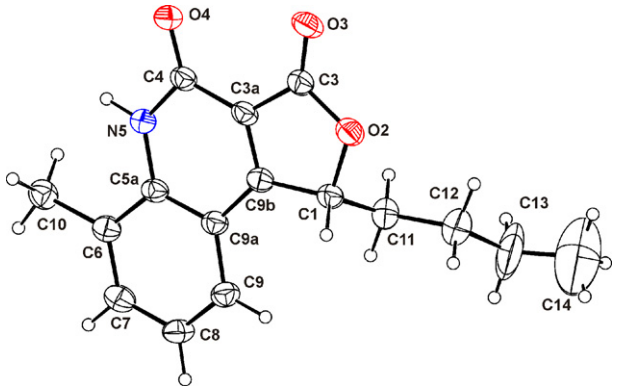


Figure 1. ORTEP plot of **2b** from the X-ray crystal structure with thermal ellipsoids at 30% probability for non-H atoms and open circles for H-atoms (O: red, N: blue). Crystals of **2b** were grown by dissolving the compound in hot *n*-butanol followed by slow cooling to room temperature.

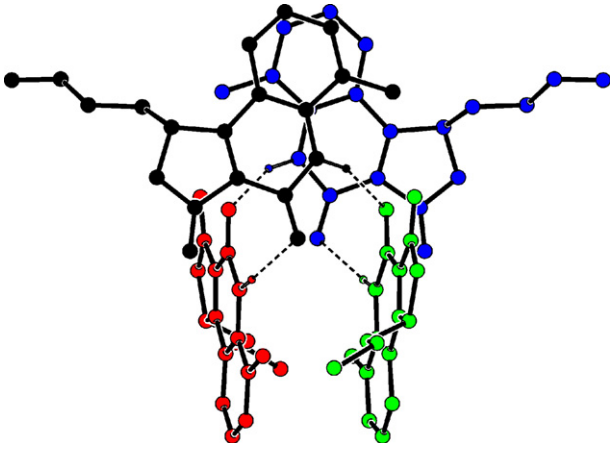
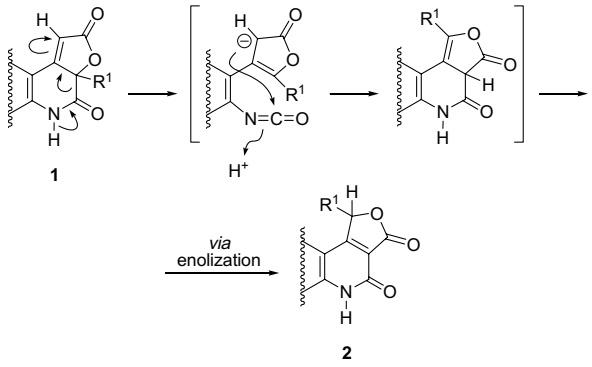


Figure 2. The hydrogen bond stacking diagram of four molecules of **2b** depicted in black, blue, red, and green. The hydrogen atoms on carbon atoms have been omitted for clarity.



Scheme 2.

that none of the N-substituted analogues **1** tested underwent the rearrangement (data not shown), but so far, attempts to provide further evidence have been unsuccessful. For example, anticipating that the intermediately formed isocyanate would be trapped as the corresponding benzylurea derivative, heating of **1c** was conducted in cyclohexylbenzene in the presence of benzylamine (2.2 equiv). Unfortunately, in comparison

to the DMAP experiment (compare entries 3 and 4 in Table 1), the yield of compound **2c** was nearly identical, and no urea derivative could be found in the reaction mixture.

In conclusion, furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-diones **1** rearranged under heating in the presence of DMAP into furo[3,4-*c*]quinoline-3,4(1*H*,5*H*)-diones **2** in moderate to good yields. To the best of our knowledge, this is the first study of such a rearrangement and the scope and limitations will be the subject of forthcoming investigations.

Acknowledgements

This study was supported by the Czech Science Foundation (Grant No. 203/07/0320), by the Ministry of Education, Youth and Sports of the Czech Republic (Project MSM7088352101 and Joint Project Nr 9-06-3) of Programme KONTAKT, and the Slovenian Research Agency (Project P1-0230-0103 and Joint Project BI-CZ/07-08-018). The authors thank Dr. Bogdan Kralj and Dr. Dušan Žigon (Mass Spectrometry Center, Jožef Stefan Institute, Ljubljana, Slovenia) for mass spectral measurements.

References and notes

1. (a) Košmrlj, J.; Kafka, S.; Leban, I.; Grad, M. *Magn. Reson. Chem.* **2007**, *45*, 700–704; (b) Klásek, A.; Lyčka, A.; Holčapek, M.; Hoza, I. *J. Heterocycl. Chem.* **2006**, *43*, 1251–1260; (c) Klásek, A.; Lyčka, A.; Holčapek, M.; Hoza, I. *Tetrahedron* **2004**, *60*, 9953–9961; (d) Klásek, A.; Mrkvička, V.; Pevec, A.; Košmrlj, J. *J. Org. Chem.* **2004**, *69*, 5646–5651; (e) Klásek, A.; Kořistek, K.; Kafka, S.; Košmrlj, J. *Heterocycles* **2003**, *60*, 1811–1820; (f) Klásek, A.; Kořistek, K.; Lyčka, A.; Holčapek, M. *Tetrahedron* **2003**, *59*, 5279–5288; (g) Klásek, A.; Polis, J.; Mrkvička, V.; Košmrlj, J. *J. Heterocycl. Chem.* **2002**, *39*, 1315–1320; (h) Kafka, S.; Klásek, A.; Polis, J.; Košmrlj, J. *Heterocycles* **2002**, *57*, 1659–1682; (i) Kafka, S.; Klásek, A.; Košmrlj, J. *J. Org. Chem.* **2001**, *66*, 6394–6399; (j) Klásek, A.; Kořistek, K.; Polis, J.; Košmrlj, J. *Tetrahedron* **2000**, *56*, 1551–1560; (k) Kafka, S.; Kovář, M.; Klásek, A.; Kappe, T. *J. Heterocycl. Chem.* **1996**, *33*, 1977–1982.
2. Klásek, A.; Kořistek, K.; Polis, J.; Košmrlj, J. *Heterocycles* **1998**, *48*, 2309–2326.
3. Klásek, A.; Kafka, S. *J. Heterocycl. Chem.* **1998**, *35*, 307–311.
4. Spectral and analytical data for new compounds **1b**,**c**,**h** and **2a**–**d**,**g**,**h** are, as follows. Compound **1b**: mp 168 °C (EtOH); IR (KBr): *v* 3265, 3112, 2963, 2942, 2912, 2869, 1743, 1719, 1632, 1598, 1492, 1465, 1441, 1389, 1351, 1320, 1249, 1233, 1203, 1165, 1140, 1134, 1093, 1072, 1014, 971, 941, 912, 901, 881, 871, 800, 780, 768, 744, 726, 707, 671, 656, 601, 560, 527, 441 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.77 (t, $J = 6.7$ Hz, 3H), 1.05–1.25 (m, 4H), 1.59–1.71 (m, 1H), 1.91–2.05 (m, 1H), 2.30 (s, 3H), 6.47 (s, 1H), 7.10 (dd, $J = 7.6$, 7.6 Hz, 1H), 7.35 (d, $J = 7.4$ Hz, 1H), 7.55 (d, $J = 7.4$ Hz, 1H), 9.94 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.6, 17.4, 21.5, 24.2, 36.5, 86.0, 112.0, 115.7, 123.2, 124.8, 125.2, 134.6, 135.4, 163.9, 167.4, 171.0; Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.05; H, 6.51; N, 5.13. Compound **1c**: mp 226–232 °C (EtOH); IR (KBr): *v* 3193, 3136, 3102, 3066, 2979, 2957, 2932, 2876, 2741, 1893, 1863, 1820, 1756, 1691, 1637, 1617, 1495, 1472, 1447, 1417, 1381, 1374, 1357, 1309, 1291, 1269, 1246, 1226, 1205, 1182, 1153, 1142, 1114, 1091, 1068, 1043, 1026, 1009, 963, 949, 934, 904, 888, 864, 831, 815, 789, 750, 739, 727, 662, 641, 619, 562, 552, 522, 465, 434 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.78 (t, $J = 6.7$ Hz, 3H), 1.15–1.22 (m, 4H), 1.58–1.69 (m, 1H), 1.92–2.03 (m, 1H), 2.31 (s, 3H), 6.43 (s, 1H), 6.97 (d, $J = 8.2$ Hz, 1H), 7.31 (dd, $J = 8.2$, 1.1 Hz, 1H), 7.53 (br s, 1H), 10.64 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.6, 20.1, 21.5, 24.2, 37.0, 86.2, 111.9, 115.2, 116.1, 127.1, 132.5, 133.8, 135.0, 163.8, 166.8, 171.0; Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.10; H, 6.40; N, 5.08. Compound **1h**: mp 246–248 °C (benzene); IR (KBr): *v* 3350–3650 (br), 3238, 3199, 3103, 2955, 2925, 1817, 1770, 1698, 1628, 1618, 1580, 1508, 1461, 1450, 1406, 1384, 1349, 1304, 1254, 1210, 1203, 1112, 1091, 1072, 1064, 1025, 1003, 970, 920, 911, 876, 857, 843, 814, 787, 760, 732, 696, 677, 655, 648, 586, 564, 495, 467, 443, 419 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.18 (s, 3H), 2.47 (s, 3H), 6.73 (s, 1H), 6.93 (d, $J = 7.8$ Hz, 1H), 7.13 (d, $J = 7.8$ Hz, 1H), 7.22–7.29 (m, 2H), 7.34–7.41 (m, 3H), 10.16 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 17.2, 19.6, 86.9, 116.0, 122.7, 125.4, 125.8, 129.2, 130.0, 133.8, 134.5, 134.9, 134.9, 161.0, 165.6, 171.0; Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 75.02; H, 5.08; N, 4.49. Compound **2a**: IR (KBr): *v* 3160, 3107, 3050, 2955, 2932, 2868, 1761, 1666,1622, 1564, 1468, 1434, 1404, 1338, 1280, 1236, 1200, 1142, 1025, 815, 768, 689, 658, 634 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, $J = 7.0$ Hz, 3H), 1.15–1.45 (m, 4H), 1.78–1.90 (m, 1H), 2.18–2.30 (m, 1H), 5.91 (dd, $J = 7.5$, 2.8 Hz, 1H), 7.32 (dd, $J = 7.9$, 7.5 Hz, 1H), 7.46 (d, $J = 8.3$ Hz, 1H), 7.73 (dd, $J = 8.3$, 7.5 Hz, 1H), 7.87 (d, $J = 7.9$ Hz, 1H), 12.13 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.6, 21.7, 26.1, 33.1, 78.3, 113.3, 114.5, 116.3, 122.6, 125.6, 134.0, 141.7, 156.5, 166.7, 166.9; HRMS calcd for $C_{15}H_{15}NO_3$: 257.1052. Found: 257.1060. Compound **2b**: IR (KBr): *v* 3315–3700 (br), 3150-3315 (br), 3138, 3078, 2956, 2929, 2873, 2863, 1769, 1673, 1619, 1605, 1578, 1500, 1468, 1399, 1344, 1209, 1165, 1139, 1039, 1012, 971, 825, 814, 782, 749, 690, 542, 519, 442 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.84 (t, $J = 7.0$ Hz, 3H), 1.15–1.45 (m, 4H), 1.78–1.90 (m, 1H), 2.18–2.40 (m, 1H), 2.48 (s, 3H), 5.91 (dd, $J = 7.5$, 3.0 Hz, 1H), 7.24 (dd, $J = 8.0$, 7.3 Hz, 1H), 7.58 (d, $J = 7.3$ Hz, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 11.19 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.7, 17.7, 21.7, 26.1, 33.2, 78.5, 113.4, 114.2, 122.4, 123.5, 124.9, 135.2, 140.1, 156.8, 166.9, 167.2; Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.60; H, 6.47; N, 5.13. Compound **2c**: IR (KBr): *v* 3310–3610 (br), 3155, 3096, 3031, 2954, 2927, 2871, 2860, 1766, 1671, 1601, 1571, 1508, 1466, 1458, 1449, 1392, 1352, 1330, 1289, 1235, 1207, 1191, 1146, 1112, 1051, 1035, 971, 958, 828, 818, 805, 758, 739, 700, 665, 639, 572, 509, 483, 447 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, $J = 7.0$ Hz, 3H), 1.16–1.45 (m, 4H), 1.77–1.90 (m, 1H), 2.18–2.30 (m, 1H), 2.40 (s, 3H), 5.87 (dd, $J = 7.6$, 3.0 Hz, 1H), 7.36 (d, $J = 8.5$ Hz, 1H), 7.56 (dd, $J = 8.5$, 1.2 Hz, 1H), 7.65 (br s, 1H), 12.06 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.7, 20.3, 21.8, 26.2, 33.1, 78.3, 113.3, 114.3, 116.2, 124.7, 131.9, 135.5, 139.8, 156.5, 166.5, 167.0; Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.63; H, 6.57; N, 5.03. Compound **2d**: IR (KBr): *v* 3154, 3100, 3047, 3028, 2976, 2938, 2901, 2870, 1777, 1673, 1622, 1603, 1565, 1507, 1472, 1434, 1403, 1337, 1277, 1240, 1195, 1156, 1137, 1056, 1025, 875, 832, 805, 768, 734, 699, 667, 625 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.24 (dd,

$J = 14.6$, 6.7 Hz, 1H), 3.60 (dd, $J = 14.6$, 3.6 Hz, 1H), 6.20 (dd, $J = 6.7$, 3.6 Hz, 1H), 7.05–7.13 (m, 2H), 7.15–7.26 (m, 3H), 7.38 (dd, $J = 7.9$, 7.5 Hz, 1H), 7.45 (d, $J = 8.3$ Hz, 1H), 7.75 (dd, $J = 8.3$, 7.5 Hz, 1H), 8.07 (d, $J = 7.9$ Hz, 1H), 12.07 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 78.2, 113.5, 114.9, 116.2, 122.6, 126.0, 126.8, 128.0, 129.4, 134.0, 135.0, 141.5, 156.3, 165.9, 166.6; HRMS calcd for $C_{18}H_{13}NO_3$: 291.0895. Found: 291.0903. Compound **2g**: IR (KBr): ν 3310–3670 (br), 3159, 3104, 3071, 3029, 3011, 2984, 2935, 2918, 2900, 2871, 2762, 2730, 1778, 1666, 1624, 1607, 1585, 1567, 1510, 1483, 1472, 1458, 1438, 1405, 1353, 1326, 1289, 1266, 1244, 1192, 1157, 1138, 1078, 1057, 1047, 1024, 992, 955, 915, 893, 887, 863, 807, 792, 777, 760, 713, 697, 662, 647, 593, 555, 519, 495, 455, 428 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.94 (s, 1H), 7.12 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.26 (d, $J = 7.7$ Hz, 1H), 7.40–7.50 (m, 6H), 7.64 (ddd, $J = 7.7$, 7.7, 1.0 Hz, 1H), 12.23 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 79.6, 113.3, 114.7, 116.3, 122.4, 125.5, 128.1, 129.2, 129.8, 134.0, 135.1, 142.0, 156.5, 165.2, 166.9; Anal. Calcd for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.83; H, 4.19; N, 4.92. Compound **2h**: IR (KBr): ν 3310–3640 (br), 3182, 3127, 3051, 2975, 2932, 1782, 1668, 1655, 1595, 1569, 1490, 1472, 1454, 1384, 1363, 1328, 1292, 1264, 1244, 1216, 1183, 1161, 1115, 1088, 1042, 1023, 1002, 992, 947, 922, 854, 830, 819, 801, 775, 753, 700, 652, 600, 590, 564, 536, 506, 494, 470, 460, 425 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18 (s, 3H), 2.46 (s, 3H), 6.88 (d, $J = 7.5$ Hz, 1H), 7.20–7.28 (m, 3H), 7.35–7.44 (m, 4H), 11.13 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 17.8, 21.7, 81.7, 114.3, 115.7, 122.6, 125.1, 128.1, 129.3, 129.6, 134.4, 135.0, 136.2, 141.3, 156.3, 165.1, 166.3; Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.47; H, 5.04; N, 4.61.

5. Crystal data for **2b**: $C_{16}H_{17}NO_3$, $M = 271.31$, tetragonal, space group $I4_1/a$ (No. 88), $a = 15.8894(5)$ Å, $c = 23.6016(10)$ Å, $V = 5958.8(4)$ Å^3, $Z = 16$, $T = 150(2)$ K, $D_c = 1.210$ g cm^{-1}, μ(Mo-Kα) = 0.084 mm^{-1}, $F(000) = 2304$, crystal size = $0.18 \times 0.18 \times 0.15$ mm, 5168 reflections collected, 2623 unique ($R_{int} = 0.0547$). The final $R_1 = 0.0706$, $wR_2 = 0.1609$, and for all data $R_1 = 0.1316$, $wR_2 = 0.1971$. Crystallographic data (excluding structure factors) for the structure of **2b** in this Letter has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 659269. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 0 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
6. Azizian, J.; Mehrdad, M.; Jadidi, K.; Sarrafi, Y. *Tetrahedron Lett.* **2000**, *41*, 5265–5268.