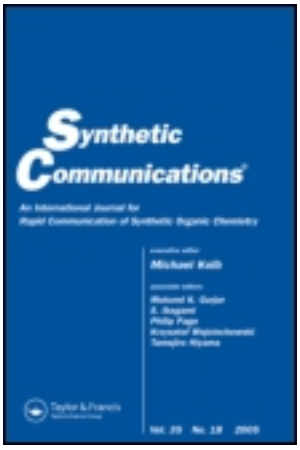

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Click Reaction: Highly Efficient Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones

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Version of record first published: 14 Oct 2008.

To cite this article: Ahmad Shaabani , Ali Maleki & Hamid Mofakham (2008): Click Reaction: Highly Efficient Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:21, 3751-3759

To link to this article: http://dx.doi.org/10.1080/00397910802213802

Synthetic Communications®, 38: 3751–3759, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802213802

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Click Reaction: Highly Efficient Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones

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Abstract: In this work, condensation reaction of 2-aminobenzamide with various alkyl, aryl, and alicyclic aldehydes or ketones to 2,3-dihydroquinazolin-4(1H)-one derivatives in the presence of a catalytic amount of ammonium chloride in ethanol at room temperature is described. This reaction can be classified as a click chemical synthesis because of its high yields, short reaction times, and green and efficient reaction medium.

Keywords: 2-Aminobenzamide, ammonium chloride, click chemistry, 2,3-dihydroquinazolin-4(1*H*)-one, green chemistry, quantitative yield

INTRODUCTION

Quinazolinone derivatives have drawn much attention because of their broad range of pharmacological activities,[1] such as anticancer,[2] anti-inflammatory,[3] and anticonvulsant[4] activities. Therefore, considerable efforts have been made to explore new, simple, and direct approaches toward the construction of 4(3*H*)-quinazolinone skeletons, for example, via amidation of 2-aminobenzonitrile followed by oxidative ring closure[5] and Pd-catalyzed heterocyclization of nitroarenes.[6]

Recently, a number of classical methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones have been reported in the literature,[7–9] involving the condensation of 2-aminobenzamide with aldehydes or ketones in the

Received May 5, 2008.
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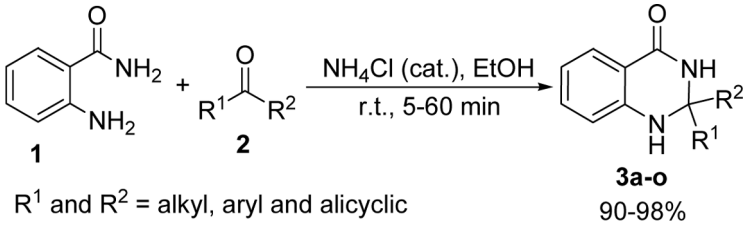


Scheme 1. Click synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives.

presence of various catalyst such as $CuCl_2$[7] and $TiCl_4$–Zn.[8] However, most of the reported methods suffer from tedious procedures and often from low yields. Therefore, the development of simpler, environmentally benign, high-yielding, and clean syntheses of 2,3-dihydroquinazolin-4(1*H*)-ones is in demand.

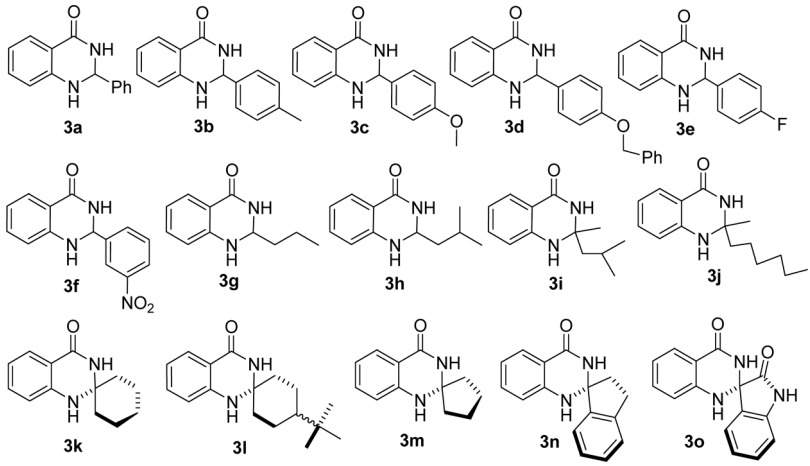
In connection with our previous work for the synthesis of pharmaceutically important heterocyclic compounds,[9] and using ammonium chloride as a catalyst in organic synthesis,[10] herein we report a quantitative yield click[11] condensation of 2-aminobenzamide **1** with an aldehyde or ketone **2** to 2,3-dihydroquinazolin-4(1*H*)-one derivatives **3a–o** in the presence of a catalytic amount of ammonium chloridein ethanol at room temperature with short reaction times (Scheme 1).

RESULTS AND DISCUSSION

In a pilot experiment, 2-aminobenzamide and benzaldehyde in EtOH were stirred at room temperature using a catalytic amount of NH_4Cl. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, an aqueous workup afforded 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one **3a** in 92% yield.

In view of the success of the reaction and to examine the scope and limitations of this approach, we applied these optimal reaction conditions to a variety of aromatic aldehydes carring electron-withdrawing and electron-donating substituents. They were condensed with 2-aminobenzamide under similar circumstances, and the products (**3b–f**) were obtained in excellent yields (Table 1, entries 2–6). Aliphatic aldehydes were also condensed with 2-aminobenzamide successfully (Table 1, entries 7 and 8). We further investigated the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from various aliphatic, alicyclic, and aromatic ketones, and they afforded the corresponding products (**3i–o**) with high yields (Table 1, entries 9–15). This reaction proceeds very cleanly, and no undesirable side reactions were observed.

Table 1. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives **(3a–o)**



Entry	Aldehyde/ketone	Product	Time (min)	Yield [a](%)
1	Benzaldehyde	**3a**	15	92
2	4-Methylbenzaldehyde	**3b**	15	94
3	4-Methoxylbenzaldehyde	**3c**	15	90
4	4-Benzyloxybenzaldehyde	**3d**	10	92
5	4-Fluorobenzaldehyde	**3e**	10	93
6	3-Nitrobenzaldehyde	**3f**	5	95
7	Butyraldehyde	**3g**	50	94
8	3-Methylbutyraldehyde	**3h**	60	97
9	3-Methyl-2-pentanone	**3i**	60	96
10	2-Octanone	**3j**	60	95
11	Cyclohexanone	**3k**	35	97
12	4-*tert*-Butylcyclohexanone	**3l**	30	98
13	Cyclopentanone	**3m**	45	96
14	2,3-Dihydroinden-1-one	**3n**	50	90
15	Isatin	**3o**	40	95

[a]Isolated yield.

The structures of the products **3a–o** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values.

In conclusion, we have developed an efficient condensation reaction of 2-aminobenzamide with various alkyl, aryl, and alicyclic aldehydes or ketones, which provides 2,3-dihydroquinazolin-4(1*H*)-one derivatives in

quantitative yields. This reaction can be classified as a new click synthesis because of its high yields, short reaction times, and green and efficient reaction medium. This synthetic route allows us to make easily a variety of 2,3-dihydroquinazolin-4(1*H*)-ones, and application of this method to generate quinazolinone-based libraries is currently under investigation in our laboratory.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra, and mass spectral data.

Typical Procedure for the Synthesis of 2,3-Dihydro-2-phenylquinazolin-4(1*H*)-one (3a)

NH_4Cl (0.027 g, 5 mol%) was added to a solution of 2-aminobenzamide (0.136 g, 1 mmol) and benzaldehyde (0.106 g, 1 mmol) in 3 mL of ethanol. The resulting mixture was stirred for 15 min at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 1/1), the product was precipitated by addition of 10 mL of water. Then, the precipitate was filtered off and washed with extra water. Finally, the residue was crystallized from acetone to give **3a** as white solid (0.206 g, 92%): mp 216–218 °C. IR (KBr) cm^{-1}: 3298, 3185, 3059, 2918, 1655, 1615, 1538, 1452. ^{1}H NMR (DMSO-d_6) δ: 5.74 (1H, br s, CH), 6.66–6.74 (2H, m, H_{arom}), 7.09–7.72 (8H, m, NH and H_{arom}), 8.26 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 67.0 (CH), 114.9, 115.4, 117.6, 127.3, 127.8, 128.8, 128.9, 133.8, 142.1, 148.3 (C_{arom}), 164.1 (CO). MS *m/z*: 224 (M^+, 28), 147 (100), 120 (72), 91 (55), 77 (37).

2,3-Dihydro-2-*p*-tolylquinazolin-4(1*H*)-one (3b)

White solid (0.224 g, 94%): mp 232–234 °C. IR (KBr) cm^{-1}: 3329, 3188, 3070, 2929, 1671, 1658, 1609, 1509, 1485. ^{1}H NMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 5.52 (1H, br s, CH), 6.47–6.52 (2H, m, H_{arom}), 7.14–7.88 (7H, m, NH and H_{arom}), 8.25 (1H, br s, NH-CO). ^{13}C NMR (DMSO-d_6) δ: 21.1 (CH), 66.2 (CH), 115.4, 115.9, 117.5, 126.3, 127.1, 128.8,

133.7, 136.9, 137.8, 147.9 (C_{arom}), 162.1 (CO). MS *m/z*: 238 (M^+, 35), 147 (100), 120 (52), 91 (50), 77 (40).

2,3-Dihydro-2-(4-methoxyphenyl)quinazolin-4(1*H*)-one (3c)

White solid (0.229 g, 90%): mp 193–195 °C. IR (KBr) cm^{-1}: 3360, 3185, 3060, 2929, 1670, 1609, 1572, 1514, 1463. ^{1}H NMR (DMSO-d_6) δ: 3.71 (s, 3H, OCH_3), 5.69 (1H, br s, CH), 6.70–7.60 (9H, m, NH and H_{arom}), 8.19 (1H, br s, NH-CO). ^{13}C NMR (DMSO-d_6) δ: 55.5 (OCH), 66.8 (CH), 114.1, 114.9, 115.4, 117.6, 127.8, 128.7, 133.7, 133.9, 148.5, 159.9 (C_{arom}), 164.2 (CO). MS *m/z*: 254 (M^+, 32), 147 (100), 120 (62), 91 (44), 77 (28).

2-(4-(Benzyloxy)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3d)

White solid (0.304 g, 92%): mp 253–254 °C. IR (KBr) cm^{-1}: 3305, 3176, 3023, 2930, 1673, 1650, 1609, 1573, 1503, 1482. ^{1}H NMR (DMSO-d_6) δ: 5.20 (s, 2H, CH_2), 6.99 (1H, br s, CH), 7.15 (2H, d, $J = 7.5$ Hz, H_{arom}), 7.20–7.60 (8H, m, NH and H_{arom}), 7.69 (1H, d, $J = 7.8$ Hz, H_{arom}), 7.78 (1H, d, $J = 6.0$ Hz, H_{arom}), 8.13 (1H, d, $J = 8.1$ Hz, NH-CO), 8.18 (2H, d, $J = 7.7$ Hz, H_{arom}). ^{13}C NMR (DMSO-d_6) δ: 68.1 (CH), 69.9 (CH_2), 115.3, 115.5, 121.2, 125.5, 126.3, 126.6, 127.8, 128.2, 128.4, 129.9, 135.0, 137.1, 149.4, 152.3 (C_{arom}), 162.8 (CO). MS *m/z*: 328 ($M^+ - 2$, 35), 119 (15), 91 (100), 65 (60), 41 (32).

2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3e)

White solid (0.225 g, 93%): mp 202–204 °C. IR (KBr) cm^{-1}: 3365, 3211, 3023, 2929, 1673, 1650, 1609, 1509, 1480. ^{1}H NMR (DMSO-d_6) δ: 5.60 (1H, br s, CH), 6.47–6.57 (2H, m, H_{arom}), 7.17–8.07 (7H, m, NH and H_{arom}), 8.26 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 66.4 (CH), 114.4, 115.9, 117.5, 126.8, 127.1, 128.8, 133.7, 136.9, 137.8, 147.8 (C_{arom}), 162.3 (CO). MS *m/z*: 242 (M^+, 35), 147 (100), 120 (42), 91 (35), 77 (26).

2,3-Dihydro-2-(3-nitrophenyl)quinazolin-4(1*H*)-one (3f)

Yellow crystals (0.256 g, 95%): mp 163–165 °C. IR (KBr) cm^{-1}: 3294, 3188, 3059, 2918, 1656, 1615, 1538, 1452. ^{1}H NMR (DMSO-d_6) δ: 5.95 (1H, br s, CH), 6.69–6.71 (1H, m, NH), 6.78 (1H, d, $J = 7.5$, H_{arom}), 7.26 (1H, m, H_{arom}), 7.35 (1H, br s, H_{arom}), 7.60–7.71 (2H, m, H_{arom}), 7.94 (1H, d, $J = 6.3$, H_{arom}), 8.19 (1H, d, $J = 6.6$, H_{arom}), 8.36 (1H, br s, H_{arom}), 8.54 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 65.6

(CH), 115.0, 115.4, 118.0, 122.0, 123.7, 127.9, 130.5, 133.8, 134.0, 144.7, 147.8, 148.1 (C_{arom}), 163.8 (CO). MS m/z: 269 (M^+, 28), 147 (100), 120 (45), 91 (70), 77 (24).

2,3-Dihydro-2-propylquinazolin-4(1*H*)-one (3g)

Colorless crystals (0.179 g, 94%): mp 162–164 °C. IR (KBr) cm^{-1}: 3322, 3175, 2932, 2855, 1658, 1512, 1452, 1394. ^1H NMR (DMSO-d_6) δ: 0.80–0.90 (3H, m, CH), 1.35–1.72 (4H, m, $2CH_2$), 5.25 (1H, m, CH), 6.57–7.15 (5H, m, NH and H_{arom}), 7.81 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 23.7 (CH_3), 29.5, 33.8 (CH_2), 64.5 (CH), 113.6, 114.4, 116.4, 127.3, 133.6, 146.6 (C_{arom}), 164.2 (CO). MS m/z: 190 (M^+, 18), 147 (100), 120 (12), 91 (45), 65 (22), 56 (30).

2,3-Dihydro-2-isobutylquinazolin-4(1*H*)-one (3h)

Light yellow crystals (0.198 g, 97%): mp 170–172 °C. IR (KBr) cm^{-1}: 3312, 3165, 2942, 2853, 1658, 1517, 1450, 1392, 1336. ^1H NMR (DMSO-d_6) δ: 0.80–0.90 (6H, m, $2CH_3$), 1.40–1.60 (2H, m, CH_2), 1.75–1.86 (1H, m, CH), 5.55–5.66 (1H, m, CH), 6.65–7.12 (5H, m, NH and H_{arom}), 7.88 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 24.5, 24.8 (CH_3), 28.8 (CH), 40.6 (CH_2), 66.9 (CH), 113.8, 114.2, 116.43, 127.5, 133.5, 146.4 (C_{arom}), 164.1 (CO). MS m/z: 204 (M^+, 10), 147 (100), 120 (14), 91 (45), 65 (15), 43 (52).

2,3-Dihydro-2-isobutyl-2-methylquinazolin-4(1*H*)-one (3i)

Colorless crystals (0.209 g, 96%): mp 173–175 °C. IR (KBr) cm^{-1}: 3326, 3170, 2932, 2858, 1650, 1512, 1452, 1390, 1326. ^1H NMR (DMSO-d_6) δ: 0.86–0.90 (6H, m, $2CH_3$), 1.34 (3H, s, CH_3), 1.42–1.59 (2H, m, CH_2), 1.78–1.90 (1H, m, CH), 6.55–6.63 (3H, m, NH and H_{arom}), 7.18 (1H, td, $J = 7.6$, 1.5 Hz, H_{arom}), 7.54 (1H, dd, $J = 6.4$, 1.2, H_{arom}), 7.88 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 23.8, 24.7, 24.9 (CH_3), 29.1 (CH), 40.8 (CH_2), 69.8 (C–NH), 113.8, 114.4, 116.4, 127.5, 133.6, 147.6 (C_{arom}), 163.5 (CO). MS m/z: 219 ($M^+ + 1$, 25), 161 (100), 120 (30), 92 (30), 65 (22), 44 (25).

2-Hexyl-2,3-dihydro-2-methylquinazolin-4(1*H*)-one (3j)

Colorless crystals (0.234 g, 95%): mp 157–159 °C. IR (KBr) cm^{-1}: 3329, 3176, 3070, 2930, 2847, 1638, 1613, 1516, 1486, 1421, 1398, 1334. ^1H

NMR (DMSO-d_6) δ: 0.80–0.84 (3H, m, CH_3), 1.20–1.27 (6H, m, $3CH_2$), 1.32 (5H, m, CH_2 and CH_3), 1.54–1.61 (2H, m, CH_2), 6.54–6.64 (3H, m, NH and H_{arom}), 7.18 (1H, td, $J = 7.6$, 1.4 Hz, H_{arom}), 7.54 (1H, d, $J = 6.7$, H_{arom}), 7.88 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 14.4, 22.4 (CH_3), 23.8, 28.4, 29.3, 31.7, 41.8 (CH_2), 69.5 (C–NH), 114.0, 114.4, 116.5, 127.5, 133.6, 147.6 (C_{arom}), 163.6 (CO). MS *m*/*z*: 247 ($M^+ + 1$, 12), 231 (48), 161 (100), 120 (46), 92 (46), 65 (26), 43 (35).

2-Spirocyclohexyl-2,3-dihydroquinazolin-4(1*H*)-one (3k)

Colorless crystals (0.215 g, 97%): mp 217–219 °C. IR (KBr) cm^{-1}: 3365, 3188, 3035, 2924, 2847, 1644, 1610, 1505, 1484, 1421, 1382, 1334. ^{1}H NMR (DMSO-d_6) δ: 1.24–1.72 (10H, m, $5CH_2$), 6.61 (1H, br s, NH), 6.80 (1H, d, $J = 7.9$ Hz, H_{arom}), 7.20 (1H, t, $J = 7.3$ Hz, H_{arom}), 7.56 (1H, d, $J = 7.4$ Hz, H_{arom}), 7.89 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 21.3, 25.1, 37.6 (CH_2), 68.2 (C_{spiro}), 114.9, 115.0, 116.9, 127.5, 133.6, 147.2 (C_{arom}), 163.7 (CO). MS *m*/*z*: 216 (M^+, 18), 173 (100), 160 (24), 120 (64), 57 (5), 45 (10).

2-Spiro(4′-*tert*-butylcyclohexyl)-2,3-dihydroquinazolin-4(1*H*)-one (3l)

Colorless crystals (0.266 g, 98%): mp 274–276 °C. IR (KBr) cm^{-1}: 3386, 3200, 3059, 2956, 2870, 1652, 1613, 1507, 1487, 1431, 1393, 1342. ^{1}H NMR (DMSO-d_6) δ: 0.80–0.89 [9H, m, $C(CH_3)_3$], 0.95–0.96 (2H, m, CH_2), 1.29–1.51 (7H, m, $3CH_2$ and CH), 6.51 (1H, br s, NH), 6.58–6.66 (2H, m, H_{arom}), 7.20 (1H, td, $J = 7.6$, 1.5 Hz, H_{arom}), 7.50 (1H, dd, $J = 7.6$, 1.2 Hz, H_{arom}), 8.11 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 22.1, 22.2 (CH_2), 28.1 ($3CH_3$), 31.2 [$C(CH_3)_3$], 32.6, 38.1 (CH_2), 47.5 (CH), 68.0 (C_{spiro}), 114.7, 114.8, 116.9, 127.7, 133.6, 147.8 (C_{arom}), 163.6 (CO). MS *m*/*z*: 272 (M^+, 12), 215 (36), 173 (100), 160 (64), 72 (20), 58 (20), 43 (34).

2-Spirocyclopentyl-2,3-dihydroquinazolin-4(1*H*)-one (3m)

Colorless crystals (0.215 g, 96%): mp 257–260 °C. IR (KBr) cm^{-1}: 3292, 3155, 3029, 2945, 2851, 1643, 1611, 1516, 1484, 1430, 1382, 1325. ^{1}H NMR (DMSO-d_6) δ: 1.65–1.79 (8H, m, $4CH_2$), 6.62–6.74 (3H, m, NH and H_{arom}), 7.20 (1H, m, H_{arom}), 7.56 (1H, d, $J = 6.5$ Hz, H_{arom}), 8.10 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 22.4 ($4CH_2$), 77.5 (C_{spiro}), 114.8, 115.0, 117.0, 127.7, 133.5, 148.0 (C_{arom}), 163.9 (CO). MS *m*/*z*: 202 (M^+, 10), 173 (100), 119 (25), 92 (20), 65 (15).

2-Spiro(2,3-dihydroinden-1-one)-2,3-dihydroquinazolin-4(1*H*)-one (3n)

Green crystals (0.225 g, 90%): mp 224–226 °C. IR (KBr) cm^{-1}: 3294, 3180, 3026, 2937, 2853, 1644, 1611, 1518, 1481, 1421, 1376. ^1H NMR (DMSO-d_6) δ: 2.34 (2H, m, CH_2), 2.95 (2H, m, CH_2), 6.64–6.67 (2H, m, NH and H_{arom}), 7.15–7.26 (6H, m, H_{arom}), 7.65 (1H, d, $J = 6.9$ Hz, H_{arom}), 8.40 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 28.2, 41.5 (CH_2), 79.0 (C_{spiro}), 114.5, 114.6, 117.2, 122.9, 125.6, 127.2, 127.6, 129.3, 133.8, 141.9, 146.6, 147.4 (C_{arom}), 163.5 (CO). MS m/z: 250 (M^+, 80), 221 (25), 173 (20), 120 (100), 92 (40), 45 (20).

2-Spiro(3-indolin-2-one)-2,3-dihydroquinazolin-4(1*H*)-one (3o)

Yellow solid (0.252 g, 95%): mp 214–216 °C. IR (KBr) cm^{-1}: 3315, 3300, 3180, 3025, 2988, 1715, 1707, 1656, 1616, 1520, 1473, 1327. ^1H NMR (DMSO-d_6) δ: 6.61–6.71 (2H, m, H_{arom}), 6.86 (1H, d, $J = 7.1$ Hz, H_{arom}), 7.05–7.34 (4H, m, NH and H_{arom}), 7.49 (1H, d, $J = 7.0$ Hz, H_{arom}), 7.61 (1H, d, $J = 7.1$ Hz, H_{arom}), 8.37 (1H, br s, NH-CO), 10.31 (1H, br s, NH–CO). ^{13}C NMR (DMSO-d_6) δ: 71.4 (C_{spiro}), 110.6, 114.3, 114.8, 117.6, 122.8, 125.8, 127.3, 129.9, 131.3, 133.8, 142.6, 147.3 (C_{arom}), 164.4, 176.5 (CO). MS m/z: 265 (M^+, 24), 221 (25), 173 (26), 120 (100), 91 (60), 55 (30).

ACKNOWLEDGMENT

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University.

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