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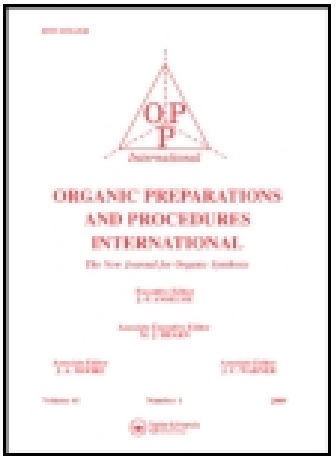

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Min Wang [a] , Zhi-Guo Song [b] & Ting-Ting Zhang [a]

[a] College of Chemistry and Chemical Engineering , Bohai University , Jinzhou, P. R. China

[b] Center for Science & Technology Experiment , Bohai University , Jinzhou, P. R. China

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Efficient Iodine-catalyzed Synthesis of 3-Aryl 4(3*H*)-quinazolinones

Min Wang,[1] Zhi-Guo Song,[2] and Ting-Ting Zhang[1]

[1]College of Chemistry and Chemical Engineering, Bohai University, Jinzhou, P. R. China
[2]Center for Science & Technology Experiment, Bohai University, Jinzhou, P. R. China

Compounds with a 4-quinazolinone motif have displayed a variety of interesting pharmacological properties such as antimalarial, antitumor, anticonvulsant, antiinflammatory, fungicidal, antimicrobial and calcilytic activities.[1–7] An examination of the literature indicates that 4-quinazolinones substituted at the 3-position are attracting the attention of chemists because they appear to have important sedative, hypnotic and anticonvulsive effects.[8] There are several methods for the preparation of this class of compounds. The most direct procedure includes the condensation of anthranilic acid, ortho esters and amines in the presence of various catalysts such as $NaHSO_4$ or Amberlyst-15,[9] Yb(III)-resin,[10] $Yb(OTf)_3$,[11] $Bi(TFA)_3$-[nbp]$FeCl_4$ ionic liquid,[12] $La(NO_3)_3 \cdot 6H_2O$ or *p*-toluenesulfonic acid,[13] Keggin-type heteropolyacid,[14] $SnCl_4 \cdot 4H_2O$,[15] and SiO_2-$FeCl_3$.[16] While this type of multi-component reaction (MCR) can produce the desired products in a single step, some of these methods have certain drawbacks such as expensive catalysts, high temperatures (60–80°C), long reaction times (20 h), and the use of harmful organic solvents. Most so-called "solvent-free" techniques still require an organic solvent such as CH_2Cl_2 during work up to remove the support, reagents or side-products. Therefore, it is desirable to develop simple, efficient, and green methods for the synthesis of 4(3*H*)-quinazolinones.

In this regard, in recent years, molecular iodine has received considerable attention as an inexpensive and easily available catalyst for various organic transformations such as esterification,[17] oxidation,[18] acetylation,[19] Hantzsch,[20] Biginelli reaction,[21] aziridination,[22] allylation,[23] Michael addition,[24] Johnson–Claisen rearrangement,[25] and Diels–Alder reactions.[26] We report the synthesis of 3-aryl 4(3*H*)-quinazolinones by the condensation of anthranilic acid **1**, ortho esters **2** and aromatic amines **3** in the presence of a catalytic amount of I_2 at room temperature without solvent (*Scheme 1*).

A model reaction of anthranilic acid with triethyl orthoformate and aniline carried out at room temperature in the absence of catalyst gave only a 5% yield after 1 h. However, a

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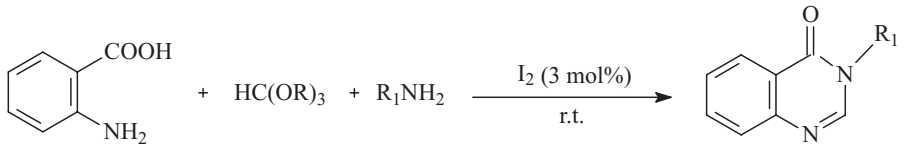
Address correspondence to Min Wang, College of Chemistry and Chemical Engineering, Bohai University, Jinzhou 121000, P. R. China. E-mail: minwangszg@yahoo.com.cn



1 **2** **3** **4 (a-o)**

Scheme 1

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quantitative yield (99%) of the product was obtained after only 40 min when 3 mol% of iodine was added. It was observed that 3 mol% of iodine catalyzed the reaction efficiently but increasing the amount of catalyst did not lead to better yields.

Table 1 illustrates the scope and generality of the reaction of anthranilic acid **1**, triethyl or trimethyl orthoformate **2**, and different aryl amines. Aryl amines carrying either electron-donating or electron-withdrawing groups reacted smoothly at room temperature and, except in the case of 2-nitroaniline, steric effects did not influence the yields significantly. Although benzylamine gave a moderate yield of the desired product (Entry **4n**), no product was

Table 1
I_2-Catalyzed Synthesis of 3-Substituted 4(3*H*)-Quinazolinones **4**(**a**-**o**)[a]

Product	R_1	Time[b] (time)[c] (min)	Yield[b] (yield)[c] (%)	mp (°C) Found	mp (°C) *lit.*[11]
4a	Ph	40 (30)	99 (92)	140–141	139–140
4b	2-MeC_6H_4	90 (120)	99 (99)	158–159	—
4c	3-MeC_6H_4	180 (360)	99 (60)	137–139	136–137
4d	4-MeC_6H_4	18 (42)	97 (87)	143–146	146–147
4e	2-$MeOC_6H_4$	40 (90)	99 (99)	151–153	—
4f	4-$MeOC_6H_4$	18 (30)	99 (92)	132–134	—
4g	2-ClC_6H_4	5 (10)	86 (78)	117–120	—
4h	4-ClC_6H_4	9 (120)	81 (90)	122–124	—
4i	4-BrC_6H_4	6 (12)	98 (82)	149–151	—
4j	2-$NO_2C_6H_4$	330 (150)	41 (45)	153–155	156–158
4k	3-$NO_2C_6H_4$	5 (2)	82 (93)	150–153	154–156
4l	4-$NO_2C_6H_4$	5 (2)	99 (99)	166–168	165–166
4m	4-$HO_2CC_6H_4$	1 (1)	87 (86)	240–242	—
4n	$PhCH_2$	2 (30)	30 (61)	154–155	—
4o	*n*-C_4H_9	1200 (1200)	0 (0)	—	—

[a]) The structures of the products were determined from spectral (IR and ^1H NMR) data and elemental analysis.
[b]) Time and yield with triethyl orthoformate.
[c]) Time and yield with trimethyl orthoformate.

obtained from *n*-butylamine (Entry **4o**). All crude products after simple washing were pure enough (testified by elemental analysis) without further purification.

In summary, we disclose here an efficient method for multi-component synthesis of 4(3*H*)-quinazolinones under mild conditions, with simple work-up, and using ethanol as the only solvent.

Experimental Section

Melting points were determined using an RY-1 micromelting point apparatus and were uncorrected. Infrared spectra were recorded on a Scimitar 2000 series Fourier Transform instrument of VARIAN. ^{1}H NMR spectra were recorded on a Bruker ARX-500 spectrometer in DMSO-d_6 using TMS as an internal standard. Elemental analyses were carried out on an EA 2400II elemental analyzer (Perkin-Elmer).

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Representative Procedure for the Synthesis of 4(a–o)

A mixture of anthranilic acid (1.371 g, 10 mmol), the orthoester (12 mmol), the amine (12 mmol), and I_2 (0.076 g, 0.3 mmol) was stirred at room temperature for an appropriate time (*Table 1*). The reaction was monitored by TLC (silica gel 60 F 254 TLC plates, cyclohexane: ethyl acetate, 1: 1 v/v). After completion of the reactions, all products were collected and washed thoroughly with EtOH during filtration and dried. All crude products thus obtained were sufficiently pure (single spot on TLC) without further purification. The obtained products were identified by IR, ^{1}H NMR, and elemental analysis. Spectral data and elemental analysis for new compounds are as follows:

3-(2-Methylphenyl)quinazolin-4(3*H*)-one (4b), white solid. IR (KBr): 1688, 1595, 1489 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.31 (d, $J = 7.2$ Hz, 1H), 7.76–7.52 (m, 2H), 7.24–7.07 (m, 5H), 2.31 (s, 3H).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.26; H, 5.12. Found: C, 76.38; H, 5.09.

3-(2-Methoxyphenyl)quinazolin-4(3*H*)-one (4e), white solid. IR (KBr): 1682, 1595, 1456 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.36 (s, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 7.45 (d, $J = 6.8$ Hz, 1H), 7.25 (t, $J = 7.0$ Hz, 1H), 7.08–7.03 (m, 2H), 6.94 (t, $J = 7.1$ Hz, 1H), 6.78 (d, $J = 8.2$ Hz, 1H), 6.54 (t, $J = 7.3$ Hz, 1H), 3.85 (s, 3H).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.80. Found: C, 71.31; H, 4.83.

3-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (4f), white solid. IR (KBr): 1717, 1591, 1454 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.54 (s, 1H), 8.05 (d, $J = 7.5$ Hz, 1H), 7.54–7.51 (m, 2H), 7.16 (t, $J = 7.5$ Hz, 1H), 6.98 (dd, $J = 8.5$, 9.5 Hz, 4H), 3.74 (s, 3H).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.80. Found: C, 71.30; H, 4.84.

3-(2-Chlorophenyl)quinazolin-4(3*H*)-one (4g), yellow solid. IR (KBr): 1667, 1601, 1415 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.01 (d, $J = 7.7$ Hz, 1H), 7.73–7.71 (m, 2H), 7.61 (t, $J = 7.6$ Hz, 1H), 7.25–7.16 (m, 2H), 6.76 (d, $J = 8.1$ Hz, 1H), 6.54 (t, $J = 7.2$ Hz, 1H).

Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91. Found: C, 65.63; H, 3.50; N, 10.88.

3-(4-Chlorophenyl)quinazolin-4(3*H*)-one (4h), pale yellow solid. IR (KBr): 1671, 1616, 1484 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.53 (s, 1H), 7.71–7.69 (m, 2H), 7.24–7.19 (m, 2H), 6.75 (d, $J = 7.5$ Hz, 2H), 6.52 (d, $J = 7.2$ Hz, 2H).

Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91. Found: C, 65.62; H, 3.51; N, 10.86.

3-(4-Bromophenyl)quinazolin-4(3*H*)-one (4i), white solid. IR (KBr): 1712, 1587, 1443 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.01 (d, $J = 7.7$ Hz, 1H), 7.60 (t, $J = 7.5$ Hz, 1H), 7.46–7.43 (m, 4H), 7.19 (d, $J = 7.5$ Hz, 2H).

Anal. Calcd. for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; N, 9.30. Found: C, 55.73; H, 3.00; N, 9.36.

3-(4-Carboxylphenyl)quinazolin-4(3*H*)-one (4m), white solid. IR (KBr): 1701, 1592, 1483 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.34 (s, 1H), 7.92–7.88 (m, 3H), 7.71 (t, $J = 8.5$ Hz, 2H), 7.63 (d, $J = 5.5$ Hz, 1H), 7.31 (d, $J = 8.5$ Hz, 1H), 6.56 (d, $J = 5.5$ Hz, 1H).

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79. Found: C, 67.77; H, 3.76.

3-Benzylquinazolin-4(3*H*)-one (4n), white solid. IR (KBr): 1678, 1621, 1459 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.52 (s, 1H), 8.00 (d, $J = 7.5$ Hz, 1H), 7.54–7.47 (m, 2H), 7.41–7.37 (m, 4H), 7.31 (t, $J = 6.8$ Hz, 1H), 7.14 (t, $J = 7.0$ Hz, 1H), 4.61 (s, 2H).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.26; H, 5.12. Found: C, 76.39; H, 5.08.

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