New Conditions for Synthesis of (±)-2-Monosubstituted and (±)-2,2-Disubstituted 2,3-Dihydro-4(1*H*)-quinazolinones from 2-Nitro- and 2-Aminobenzamide

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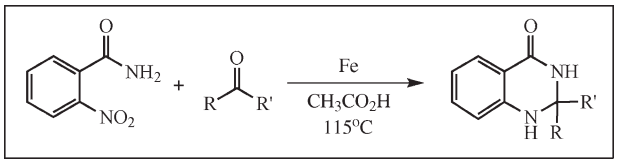
Received June 8, 2010
DOI 10.1002/jhet.672
Published online 21 April 2011 in Wiley Online Library (wileyonlinelibrary.com).



An efficient synthesis of (±)-2-monosubstituted and (±)-2,2-disubstituted 2,3-dihydro-4(1*H*)-quinazolinones has been developed using a dissolving metal reduction-condensative cyclization strategy. Treatment of 2-nitrobenzamide and an aldehyde or ketone with iron powder in refluxing acetic acid affords high yields of the title compounds. More complex ring systems are available by incorporating additional reactive functionality γ to the carbonyl of the aldehyde or ketone substrate. The scope and limitations of the process along with optimized procedural details are presented. The same target molecules are also accessible by reaction of 2-aminobenzamide with aldehydes and ketones in refluxing acetic acid.

J. Heterocyclic Chem., **48**, 991 (2011).

INTRODUCTION

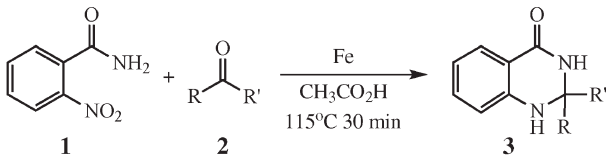
Dihydroquinazolinones are an important class of heterocycles that have expressed a broad spectrum of biological activities [1]. This ring system is found as the core structure in compounds investigated as anticancer [2], anti-inflammatory [3], anticonvulsant [4], antibacterial [5], antifungal [6], anti-osteoporosis [7], and diuretic [8] drug candidates. Additionally, several dihydroquinazolinone derivatives have been found to be potent plant growth regulators and herbicidal agents [9].

We have previously utilized tandem reactions initiated by dissolving metal reduction of nitroarenes to prepare indole-3-carboxylic esters [10] and benzo-fused oxepinones, diazepinones, [11] and carbazoles [12] as well as various linear-fused ring systems [13]. In this project, we have used a tandem reduction-condensative cyclization strategy involving 2-nitrobenzamide (**1**) and aldehydes **2a–h** or ketones **2i–o** for the formation of 2-monosubstituted and 2,2-disubstituted 2,3-dihydro-4(1*H*)-quinazolinones **3**. This method has been further extended to include sequences involving additional reactions following the initial heterocyclic ring closure. Additionally, we have found that heating 2-aminobenzamide (**4**) with aldehydes and ketones in glacial acetic acid also provides the target heterocycles cleanly and in high yield.

Earlier methods to prepare dihydroquinazolinones have reacted **1** with aldehydes and ketones in the presence of titanium(IV) chloride and zinc [14], samarium iodide [15] and samarium in the presence of iodine [16]. The target compounds have also been prepared by condensation of **4** with aldehydes or ketones in the presence of catalysts such as gallium(III) triflate [17], scandium(III) triflate [18] or by heating in solvents such as trifluoroethanol [19]. Most of these reagents and catalysts are expensive and require dry box conditions; additionally, the reaction workup procedures are often tedious. An alternative approach has been reported using isatoic anhydride with amines and carbonyl compounds in the presence of montmorillonite K-10 [20], *p*-toluenesulfonic acid [21], Amberlyst-15 under microwave conditions [22], and aluminum tris(dihydrogenphosphate) [23], but the yields were slightly lower (*ca* 5% on average) than those in this work, and each procedure was evaluated using only aryl aldehydes. To expand on this foundation, we report modified conditions, which use inexpensive, readily available reagents to afford dihydroquinazolinones from a wide variety of aldehydes and ketones. The only general procedure that yields comparable results involves the cyclization of **4** with aldehydes and ketones promoted by catalytic ammonium chloride in ethanol [24].

RESULTS AND DISCUSSION

The results of our tandem synthesis of dihydroquinazolinones from reductive cyclization of **1** with aldehydes and ketones are summarized in Figure 1. The current reaction is performed by reacting a 1:1 mole ratio of 2-nitrobenzamide (**1**) and the carbonyl compound **2** with five equivalents of iron powder in acetic acid at 115°C for 30 min. After quenching with water, extractive workup

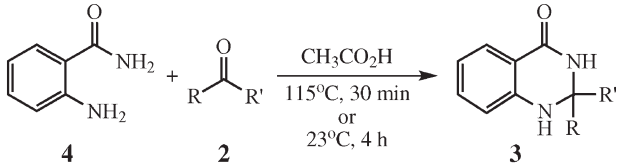


1 **2** **3**

	R	R'	Yield of **3** (%)
Aldehydes			
a	C_6H_5	H	90
b	4-$CH_3OC_6H_4$	H	90
c	4-$CF_3C_6H_4$	H	89
d	2-ClC_6H_4	H	93
e	$CH_3CH_2CH_2CH_2$	H	94
f	(*E*)-C_6H_5CH=CH	H	89
g	$CH_3CH_2O_2C(CH_2)_3$	H	78
h	$CH_3CH_2O_2C(CH_2)_4$	H	73
Ketones			
i	CH_3	CH_3	95
j	$CH_3CH_2CH_2$	CH_3	90
k	C_6H_5	CH_3	86
l	$C_6H_5CH_2$	CH_3	91
m	C_6H_5	C_6H_5	60
n	$(CH_2)_4$		93
o	$(CH_2)_5$		92

Figure 1. Cyclization of aldehydes and ketones with **1**.

and recrystallization from ethanol, dihydroquinazolinones **3** are isolated in pure form. Only rarely is chromatographic purification required (e.g., **3g** and **3h**). Alternatively, the target heterocycles can also be pre-

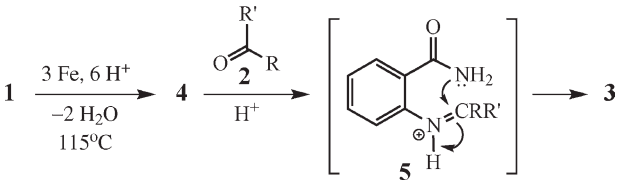


4 **2** **3**

Carbonyl Substrate	Yield of **3** (%)
Aldehydes	
2a	90
2b	90
2d	92
2g	76
Ketones	
2i	92
2j	90
2l	88
2m	56
2o	90

Figure 2. Cyclization of aldehydes and ketones with **4**.

Scheme 1. Mechanism for dihydroquinazolinone formation.

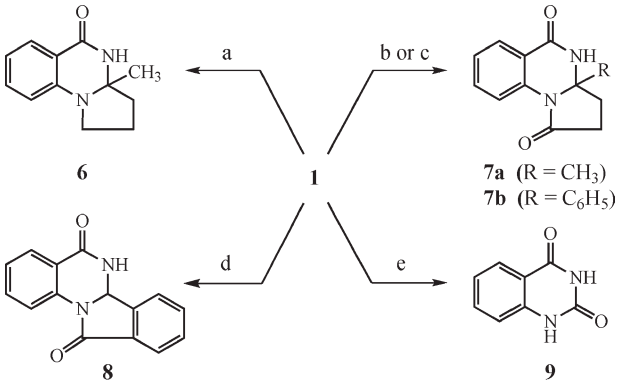


pared in comparable yields by reacting 2-aminobenzamide (**4**) with an aldehyde or ketone (1:1) in acetic acid at 115°C for 30 min or 23°C for 4 h (see Fig. 2).

The reaction sequence from **1** begins with dissolving metal reduction of the nitro function to give **4**. The resulting amino group then reacts with the aldehyde or ketone in **2** to form an iminium intermediate **5**, which is attacked by the amide nitrogen to close the heterocyclic portion of the structure. Reactions starting with **4** do not require added iron and proceed rapidly at 115°C or more slowly at 23°C (see Scheme 1). Thus, the iron is only important for the reduction process and is not required for the ring closure.

Further studies sought to extend the tandem reaction sequence to generate more complex structures such as **6–9** by using aldehydes and ketones bearing a second reactive group γ to the carbonyl function (see Scheme 2). Cyclization of **1** with these substrates would yield dihydroquinazolinones with functionality δ to the aniline nitrogen such that a subsequent reaction would close a five-membered ring. For example, the reaction of **1** with 5-chloro-2-pentanone (**10**) under dissolving metal conditions furnished tetrahydropyrrolo[1,2-*a*]quinazolinone **6** in 73% yield [25]. This reaction involved reduction of the nitro function and ring closure to generate the dihydroquinazolinone bearing a chloride leaving group δ to the aniline nitrogen. Subsequent S_N2 displacement of

Scheme 2. Preparation of more complex systems from **1** [a].



6 **1** **7a** (R = CH_3) **7b** (R = C_6H_5) **8** **9**

[a] Key: Fe, CH_3CO_2H, 115°C in the presence of (a) 5-chloro-2-pentanone (**10**), 73%; (b) **7a**: methyl levulinate (**11**), 74%; (c) **7b**: methyl 3-benzoylpropionate (**12**), 77%; (d) methyl 2-formylbenzoate (**13**), 72%; (e) diphosgene (**14**), 86%.

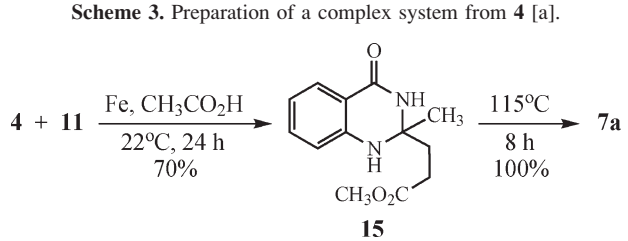
chloride by the more reactive aniline nitrogen [26] then delivered the final tricyclic product. The extremely mild nature of the reduction conditions was evidenced by the fact that no hydrogenolysis of the aliphatic chloride was observed [27]. A second extended sequence resulted when **1** was reacted with γ-ketoesters such as methyl levulinate (**11**) or methyl 3-benzoylpropionate (**12**). These reactions proceeded to give reduction, condensative ring closure and cyclization by addition-elimination of the aniline nitrogen with the δ ester groups to give tetrahydropyrrolo[1,2-*a*]quinazolin-1,5-diones **7a** and **7b** in 74% and 77% yields, respectively [28]. It should be noted that five-membered rings were the only ones that could be successfully formed in the final step of these extended tandem reactions. Oxoesters with greater separation between the carbonyl moieties (e.g., **2g** and **2h**) failed to undergo the final cyclization, even after refluxing for an additional 24 h. In a related transformation, **1** was reduced in the presence of methyl 2-formylbenzoate (**13**) [29] to produce 6,6a-dihydroisoindolo[2,1-*a*]quinazolin-5,11-dione (**8**) in 72% yield. Finally, **1** was also reacted with diphosgene (**14**) to afford 2,4(1*H*,3*H*)-quinazolinedione (**9**) in 86% yield.

One extended reaction was investigated using **4** as the starting material (see Scheme 3). Treatment of **4** with **11** in acetic acid at 23°C for 24 h gave (±)-methyl 3-(1,2,3,4-tetrahydro-2-methyl-4-oxoquinazolin-2-yl)propanoate (**15**) in 70% yield. Further heating of **15** in acetic acid at 115°C for 8 h then effected quantitative ring closure to **7a**. This two-step synthesis could be simplified to a one-step process by running the reaction at 115°C. In the reaction of **1** with **11** under dissolving metal conditions at 115°C, intermediate **15** could not be isolated.

CONCLUSIONS

We have developed efficient one-pot syntheses of (±)-2-monosubstituted and (±)-2,2-disubstituted 2,3-dihydro-4(1*H*)-quinazolinones from 2-nitro- and 2-aminobenzamide. The procedures utilize inexpensive reagents, mild conditions, and simple laboratory procedures. The method furnishes high yields of the title compounds from a wide range of aldehydes and ketones without the need for extensive purification. This method can be extended to the synthesis of more complex structures by positioning additional functionality γ to the carbonyl of the aldehyde or ketone (δ to the aniline nitrogen in the initially formed dihydroquinazolinone) so that subsequent reactions can occur.

Scheme 3. Preparation of a complex system from **4** [a].



EXPERIMENTAL

All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech No 21521). Commercial reagents and solvents were used as received. Preparative separations were performed using flash column chromatography [30] on silica gel (Grade 62, 60–200 mesh) mixed with UV-active phosphor (Sorbent Technologies No UV-5); band elution was monitored using a hand-held UV lamp. Melting points were uncorrected. FT-IR spectra were run as thin films on sodium chloride disks. Unless otherwise indicated, ^{1}H- and ^{13}C-NMR spectra were measured in dimethyl sulfoxide-d_6 at 300 MHz and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (*J*) are reported in Hz. Low-resolution mass spectra (electron impact/direct probe) were run at 70 eV or 30 eV as indicated.

Representative procedure from 2-nitrobenzamide: (±)-2,3-Dihydro-2-phenyl-4(1*H*)-quinazolinone (3a). A 100-mL three-necked round-bottomed flask, equipped with a reflux condenser, a magnetic stirrer, and a nitrogen inlet, was charged with 9 mL of glacial acetic acid, 498 mg (3.00 mmoles) of 2-nitrobenzamide (**1**), and 318 mg (3.00 mmoles) of benzaldehyde (**2a**). The flask was placed in an oil bath preheated to 105°C to dissolve the reactants. The heat was briefly removed, 840 mg (15.0 mmoles, 5 equiv.) of iron powder (>100 mesh) was added, and the reaction was refluxed for 30 min. [Caution! The addition was sufficiently exothermic to boil the mixture and some frothing occurred as the iron was added. The reaction flask should be at least 10 times the volume of the reactants at this scale.] The reaction mixture was cooled, poured into saturated aqueous sodium chloride, and extracted with ether (1 × 50 mL) and ethyl acetate (1 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (two times) and saturated aqueous sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum to give a light tan solid. Recrystallization of the crude product from ethanol then gave 610 mg (90%) of **3a** as a white solid, mp 220–221°C (ref. 24; mp 218–220°C). IR: 3302, 3185, 1652, 1611 cm^{-1}; ^{1}H-NMR: δ 8.29 (br s, 1H), 7.61 (d, 1H, *J* = 7.8), 7.49 (d, 2H, *J* = 7.0), 7.42–7.32 (complex, 3H), 7.24 (td, 1H, *J* = 7.6, 1.6), 7.11 (br s, 1H), 6.75 (d, 1H, *J* = 8.0), 6.67 (t, 1H, *J* = 7.6), 5.75 (s, 1H); ^{13}C-NMR: δ 163.6, 147.9, 141.6, 133.3, 128.4, 128.3, 127.3, 126.8, 117.1, 114.9, 114.4, 66.5; ms (30 eV): *m/z* 224 (M^+).

(±)-2,3-Dihydro-2-(4-methoxyphenyl)-4(1*H*)-quinazolinone (3b). This was prepared from 498 mg (3.00 mmoles) of **1**, 408 mg (3.00 mmoles) of 4-methoxybenzaldehyde (**2b**), and 840 mg (15.0 mmoles) of iron powder in 9 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3b** (686 mg, 90%) was isolated as a white solid, mp 192–193°C (ref. 24; mp 193–195°C). IR: 3300, 3188, 1655, 1609 cm^{-1}; ^{1}H-NMR: δ 8.17 (br s, 1H), 7.61 (d, 1H, *J* = 6.6), 7.41 (d, 2H, *J* = 8.6), 7.23 (td, 1H, *J* = 7.6, 1.4), 6.99 (br s, 1H), 6.94 (d, 2H, *J* = 8.6), 6.72 (d, 1H, *J* = 8.2), 6.67 (t, 1H, *J* = 7.7),

5.70 (s, 1H), 3.74 (s, 3H); ^{13}C-NMR: δ 163.4, 159.4, 148.0, 133.4, 133.2, 128.2, 127.3, 117.0, 115.0, 114.4, 113.6, 66.3, 55.1; ms (30 eV): *m/z* 254 (M^+).

(±)-2,3-Dihydro-2-[4-(trifluoromethyl)phenyl]-4(1*H*)-quinazolinone (3c). This compound was prepared from 498 mg (3.00 mmoles) of **1**, 522 mg (3.00 mmoles) of 2-(trifluoromethyl)benzaldehyde (**2c**), and 840 mg (15.0 mmoles) of iron powder in 9 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3c** (779 mg, 89%) was isolated as a white solid, mp 194–196°C. IR: 3285, 3187, 1648, 1618 cm^{-1}; ^{1}H-NMR: δ 8.46 (d, 1H, *J* = 1.3), 7.78 (d, 2H, *J* = 8.2), 7.72 (d, 2H, *J* = 8.2), 7.63 (dd, 1H, *J* = 7.7, 1.1), 7.26 (overlapping td, 1H, *J* = 7.1, 1.1 and br s, 1H), 6.77 (d, 1 H, *J* = 7.7), 6.69 (t, 1H, *J* = 7.7), 5.88 (d, 1H, *J* = 1.3); ^{13}C-NMR: δ 163.4, 147.5, 146.4, 133.5, 129.0, 128.9 (q, *J* = 31.7), 127.7 (2C), 127.4, 125.3 (q, *J* = 3.7), 124.2 (q, *J* = 271.6), 117.4, 114.9, 114.5, 65.7; ms (30 eV): *m/z* 292 (M^+). Anal. Calcd. for $C_{15}H_{11}F_3N_2O$: C, 61.64; H, 3.79; N, 9.59. Found: C, 61.58; H, 3.81; N, 9.56.

(±)-2-(2-Chlorophenyl)-2,3-dihydro-4(1*H*)-quinazolinone (3d). This compound was prepared from 498 mg (3.00 mmoles) of **1**, 421 mg (3.00 mmoles) of 2-chlorobenzaldehyde (**2d**), and 840 mg (15.0 mmoles) of iron powder in 9 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3d** (721 mg, 93%) was isolated as an off-white solid, mp 205–206°C. IR: 3286, 3192, 1645, 1614 cm^{-1}; ^{1}H-NMR: δ 8.20 (s, 1 H), 7.65 (d, 1 H, *J* = 6.6), 7.50 (m, 1H), 7.40 (m, 2H), 7.26 (t, 2H, *J* = 7.1), 7.00 (s, 1H), 6.74 (m, 2H); ^{13}C-NMR: δ 163.6, 147.6, 137.8, 133.4, 131.8, 130.2, 129.5, 128.7, 127.4, 127.3, 117.4, 114.6, 114.5, 63.6; ms (30 eV): *m/z* 258, 260 (M^+:M^++2, 3:1). Anal. Calcd. for $C_{14}H_{11}ClN_2O$: C, 64.99; H, 4.29; N, 10.83. Found: C, 65.03; H, 4.28; N, 10.79.

(±)-2-Butyl-2,3-dihydro-4(1*H*)-quinazolinone (3e). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 172 mg (2.00 mmoles) of pentanal (**2e**), and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3e** (383 mg, 94%) was isolated as a white solid, mp 143–144°C (ref 15; mp 144–146°C). IR: 3293, 1651, 1614 cm^{-1}; ^{1}H-NMR: δ 7.90 (br s, 1H), 7.58 (d, 1H, *J* = 7.7), 7.23 (t, 1H, *J* = 7.7), 6.73 (d, 1H, *J* = 7.7), 6.65 (t, 1H, *J* = 7.7), 6.58 (br s, 1H), 4.69 (s, 1H), 1.62 (m, 2H), 1.40 (m, 2H), 1.30 (m, 2H), 0.88 (t, 3H, *J* = 6.8); ^{13}C-NMR: δ 163.9, 148.5, 133.0, 127.3, 116.8, 115.0, 114.3, 64.4, 34.7, 25.4, 22.1, 13.9; ms (70 eV): *m/z* 147 (M^+-C_4H_9).

(±)-2,3-Dihydro-2-[(1*E*)-2-phenylethenyl]-4(1*H*)-quinazolinone (3f). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 264 mg (2.00 mmoles) of *trans*-cinnamaldehyde (**2f**), and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3f** (445 mg, 89%) was isolated as a yellow solid, mp 170–173°C (ref. 7; mp 168–172°C). IR: 3276, 1651, 1611 cm^{-1}; ^{1}H-NMR: δ 8.16 (br s, 1H), 7.63 (d, 1H, *J* = 7.7), 7.46 (d, 2H, *J* = 8.2), 7.35 (t, 2H, *J* = 7.7), 7.26 (m, 2H), 6.90 (s, 1H), 6.76 (d, 1H, *J* = 8.2), 6.68 (d, 1H, *J* = 15.9), 6.67 (d, 1H, *J* = 7.7), 6.38 (dd, 1H, *J* = 15.9, 6.6), 5.31 (d, 1H, *J* = 6.6); ^{13}C-NMR: δ 163.3, 147.8, 135.7, 133.2, 131.6, 128.7, 128.3, 128.1, 127.4, 126.6, 117.1, 114.8, 114.5, 65.8; ms (30 eV): *m/z* 250 (M^+).

(±)-Ethyl 4-(1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)butanoate (3g). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 288 mg (2.00 mmoles) of ethyl 5-oxopentanoate (**2g**) [31], and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3g** (408 mg, 78%) was isolated as a white solid following flash chromatography on a 30 cm × 2 cm silica gel column eluted with 50% ether in hexanes containing 1% methanol, mp 106–108°C. IR: 3302, 3204, 1731, 1661, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.87 (d, 1 H, *J* = 7.7), 7.30 (t, 1H, *J* = 7.7), 7.04 (br s, 1H), 6.84 (t, 1H, *J* = 7.7), 6.69 (d, 1 H, *J* = 8.2), 4.91 (s, 1 H), 4.49 (br s, 1H), 4.14 (q, 2 H, *J* = 7.1), 2.39 (m, 2H), 1.82 (m, 4H), 1.26 (t, 3H, *J* = 7.1); ^{13}C-NMR ($CDCl_3$): δ 173.2, 165.5, 147.3, 133.8, 128.4, 119.2, 115.8, 114.8, 64.9, 60.6, 34.7, 33.5, 19.1; ms (30 eV): *m/z* 262 (M^+). Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.12; H, 6.87; N, 10.69. Found: C, 64.23; H, 6.91; N, 10.63. Extended heating of this reaction for 24 h failed to induce further cyclization.

(±)-Ethyl 5-(1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)pentanoate (3h). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 316 mg (2.00 mmoles) of ethyl 6-oxohexanoate (**2h**) [32], and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3h** (402 mg, 73%) was isolated as a white solid following flash chromatography on a 30 cm × 2 cm silica gel column eluted with 50% ether in hexanes containing 1% methanol, mp 110–113°C. IR: 3307, 3203, 1736, 1643, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.88 (d, 1H, *J* = 7.7), 7.31 (t, 1H, *J* = 7.7), 6.86 (t, 1H, *J* = 7.7), 6.69 (d, 1H, *J* = 8.2), 6.24 (br s, 2H), 4.91 (t, 1H, *J* = 5.8), 4.14 (q, 2H, *J* = 7.1), 2.35 (t, 2H, *J* = 7.1), 1.80 (q, 2H, *J* = 7.1), 1.69 (quintet, 2H, *J* = 7.1), 1.51 (m, 2H), 1.26 (t, 3H, *J* = 7.1); ^{13}C-NMR ($CDCl_3$): δ 173.4, 165.4, 147.4, 133.7, 128.4, 119.2, 115.8, 114.7, 65.0, 60.4, 35.0, 33.8, 24.3, 23.4, 14.2; ms (30 eV): *m/z* 276 (M^+). Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.22; H, 7.24; N, 10.14. Found: C, 65.31; H, 7.27; N, 10.08. Extended heating of this reaction for 24 h failed to induce further cyclization.

2,3-Dihydro-2,2-dimethyl-4(1*H*)-quinazolinone (3i). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 116 mg (2.00 mmoles) of acetone (**2i**), and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3i** (334 mg, 95%) was isolated as a white solid, mp 182–183°C (ref. 33; mp 183–184°C). IR: 3260, 3172, 1640, 1614 cm^{-1}; ^{1}H-NMR: δ 7.94 (br s, 1H), 7.57 (d, 1H, *J* = 8.2), 7.20 (t, 1H, *J* = 7.7), 6.63 (br s, 1H), 6.62 (d, 1H, *J* = 8.2), 6.61 (t, 1H, *J* = 7.7), 1.36 (s, 6H); ^{13}C-NMR: δ 163.1, 147.1, 133.2, 127.2, 116.4, 114.2, 113.8, 66.8, 29.0; ms (70 eV): *m/z* 161 (M^+-CH_3).

(±)-2,3-Dihydro-2-methyl-2-propyl-4(1*H*)-quinazolinone (3j). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 172 mg (2.00 mmoles) of 2-pentanone (**2j**), and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3j** (367 mg, 90%) was isolated as a white solid, mp 192–195°C. IR: 3272, 3184, 1645, 1613 cm^{-1}; ^{1}H-NMR: δ 7.90 (br s, 1H), 7.56 (d, 1H, *J* = 7.7), 7.20 (td, 1H, *J* = 8.2, 1.6), 6.64 (d, 1H, *J* = 8.2), 6.59 (br s, 1H), 6.59 (t, 1H, *J* = 7.7), 1.60 (m, 2H), 1.35 (m, 2H), 1.34 (s, 3H), 0.84 (t, 3H, *J* = 7.1); ^{13}C-NMR: δ 163.1, 147.2, 133.1, 127.1, 116.0, 113.9, 113.5, 69.0, 43.7, 27.9, 16.7, 14.1; ms (70 eV): *m/z* 161 (M^+-C_3H_7).

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.59; H, 7.84; N, 13.73. Found: C, 70.64; H, 7.86; N, 13.70.

(±)-2,3-Dihydro-2-methyl-2-phenyl-4(1*H*)-quinazolinone (3k). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 240 mg (2.00 mmoles) of acetophenone (**2k**), and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3k** (409 mg, 86%) was isolated as a white solid, mp 222–224°C. IR: 3297, 3182, 1651, 1611 cm^{-1}; ^{1}H-NMR: δ 8.76 (br s, 1H), 7.63 (br s, 1H), 7.48 (m, 3H), 7.28 (d, 2H, J = 7.4), 7.19 (m, 2H), 6.77 (d, 1H, J = 8.0), 6.57 (t, 1H, J = 7.1), 1.64 (s, 3H); ^{13}C-NMR: δ 163.8, 147.7, 147.2, 133.3, 127.9, 127.2, 127.0, 125.1, 116.8, 115.0, 114.3, 70.1, 30.7; ms (70 eV): m/z 223 (M^+-CH_3). Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.76. Found: C, 75.61; H, 5.89; N, 11.73.

(±)-2-Benzyl-2,3-dihydro-2-methyl-4(1*H*)-quinazolinone (3l). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 268 mg (2.00 mmoles) of phenylacetone (**2l**), and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3l** (458 mg, 91%) was isolated as a white solid, mp 162–165°C. IR: 3292, 1655, 1615 cm^{-1}; ^{1}H-NMR: δ 7.96 (br s, 1H), 7.50 (d, 1H, J = 7.7), 7.22 (m, 3H), 7.15 (d, 2H, J = 7.1), 6.71 (br s, 1H), 6.65 (d, 1H, J = 8.2), 6.57 (t, 1H, J = 7.7), 2.93 (d, 1H, J = 13.2), 2.83 (d, 1H, J = 13.2), 1.37 (s, 3H); ^{13}C-NMR: δ 163.0, 146.8, 136.5, 133.2, 130.7, 127.7, 127.0, 126.2, 116.1, 114.0, 113.6, 69.3, 46.5, 27.5; ms (70 eV): m/z 161 (M^+-C_7H_7). Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; H, 11.11. Found: C, 76.24; H, 6.36; N, 11.05.

2,3-Dihydro-2,2-diphenyl-4(1*H*)-quinazolinone (3m). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 364 mg (2.00 mmoles) of benzophenone (**2m**), and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3m** (360 mg, 60%) was isolated as a white solid, mp 203–205°C. IR: 3378, 3281, 1650, 1614 cm^{-1}; ^{1}H-NMR: δ 7.80 (d, 1H, J = 7.7), 7.38 (m, 4H), 7.30 (m, 7H), 6.77 (t, 1H, J = 7.7), 6.70 (d, 1H, J = 8.2), 6.60 (br s, 1H), 5.25 (br s, 1H); ^{13}C-NMR: δ 164.1, 145.5, 143.6, 134.1, 128.6, 128.4 (2C), 127.2, 119.2, 115.4, 114.8, 75.9; ms (30 eV) 300 (M^+). Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 80.00; H, 5.33; N, 9.33. Found: C, 79.88; H, 5.37; N, 9.26.

Spiro[cyclopentane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3n). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 168 mg (2.00 mmoles) of cyclopentanone (**2n**), and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3n** (374 mg, 93%) was isolated as an off-white solid, mp 258–259°C (ref. 24; mp 257–260°C). IR: 3289, 3162, 1638, 1613 cm^{-1}; ^{1}H-NMR: δ 8.10 (br s, 1H), 7.59 (d, 1H, J = 7.7), 7.22 (t, 1H, J = 7.7), 6.75 (br s, 1H), 6.70 (d, 1H, J = 8.2), 6.63 (t, 1H, J = 7.7), 1.80 (s, 4H), 1.67 (s, 4H); ^{13}C-NMR: δ 163.4, 147.5, 133.0, 127.2, 116.5, 114.6, 114.3, 77.1, 39.3, 22.0; ms (30 eV): m/z 202 (M^+).

Spiro[cyclohexane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3o). This compound was prepared from 332 mg (2.00 mmoles) of **1**, 196 mg (2.00 mmoles) of cyclohexanone (**2o**), and 560 mg (10.0 mmoles) of iron powder in 7 mL of acetic acid using the procedure outlined for the preparation of **3a**. Product **3o** (396 mg, 92%) was isolated as an off-white solid, mp 216–218°C (ref. 24; mp 217–219°C). IR: 3287, 1651, 1613 cm^{-1}; ^{1}H-NMR: δ 7.94 (br s, 1H), 7.57 (d, 1H, J = 7.7), 7.22 (td, 1H, J = 8.2, 1.1), 6,82 (d, 1H, J = 8.2), 6.62 (t, 1H, J = 7.1), 6.62 (br s, 1H), 1.74 (m, 2H), 1.61 (m, 2H), 1.58 (m, 4H), 1.42 (m, 1H), 1.25 (m, 1H); ^{13}C-NMR: δ 163.2, 146.8, 133.1, 127.1, 116.5, 114.6, 114.4, 67.8, 37.2, 24.7, 20.9; ms (30 eV): m/z 216 (M^+).

(±)-3a-Methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (6). This compound was prepared from 415 mg (2.50 mmoles) of **1**, 301 mg (2.50 mmoles) of 5-chloro-2-pentanone (**10**), and 698 mg (12.5 mmoles) of iron powder in 8 mL of acetic acid using the procedure outlined for the preparation of **3a** with the reflux period extended to 8 h. Product **6** (368 mg, 73%) was isolated directly from the reaction as a white solid, mp 163–165°C (ref. 25; mp 165–167°C). IR: 3190, 1660, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.92 (dd, 1H, J = 7.7, 1.1), 7.36 (td, 1H, J = 7.7, 1.6), 7.04 (br s, 1H), 6.78 (t, 1H, J = 7.1), 6.59 (d, 1H, J = 8.2), 3.50 (m, 2H), 2.17 (m, 2H), 2.04 (m, 1H), 1.39 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 164.9, 145.3, 134.0, 128.6, 117.3, 114.9, 113.8, 74.9, 47.1, 39.6, 25.6, 21.8; ms (30 eV): m/z 202 (M^+). Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 71.29; H, 6.93; N, 13.86. Found: 71.33; H, 6.94; N, 13.83.

(±)-2,3,3a,4-Tetrahydro-3a-methylpyrrolo[1,2-*a*]quinazoline-1,5-dione (7a). This compound was prepared from 415 mg (2.50 mmoles) of **1**, 325 mg (2.50 mmoles) of methyl levulinate (**11**), and 698 mg (12.5 mmoles) of iron powder in 8 mL of acetic acid using the procedure outlined for the preparation of **3a** with the reflux period extended to 8 h. Product **7a** (400 mg, 74%) was isolated as a pale yellow solid following purification by flash chromatography on a 30 cm × 2 cm silica gel column eluted with 50% ether in hexanes containing 2% methanol, mp 175–177°C (ref. 28; mp 179–180°C). IR: 3321, 1712, 1669, 1604 cm^{-1}; ^{1}H-NMR: δ 8.25 (br s, 1H), 8.16 (d, 1H, J = 8.2), 8.06 (dd, 1H, J = 7.8, 1.4), 7.59 (td, 1H, J = 7.8, 1,4), 7.29 (t, 1H, J = 8.2), 2.71 (m, 2H), 2.40 (m, 2H), 1.58 (s, 3H); ^{13}C-NMR: δ 171.7, 163.5, 135.8, 133.8, 128.2, 125.0, 120.7, 119.5, 74.5, 32.9, 30.0, 26.9; ms (30 eV): m/z 216 (M^+).

(±)-2,3,3a,4-Tetrahydro-3a-phenylpyrrolo[1,2-*a*]quinazoline-1,5-dione (7b). This compound was prepared from 415 mg (2.50 mmoles) of **1**, 480 mg (2.50 mmoles) of methyl 3-benzoylpropionate (**12**), and 698 mg (12.5 mmoles) of iron powder in 8 mL of acetic acid using the procedure outlined for the preparation of **3a** with the reflux period extended to 8 h. Product **7b** (536 mg, 77%) was isolated as a pale yellow solid following flash chromatography on a 30 cm × 2 cm silica gel column eluted with 50% ether in hexanes containing 2% methanol, mp 290°C (decomposition) (ref. 28; mp >290°C). IR: 3203, 1716, 1668, 1604 cm^{-1}; ^{1}H-NMR: δ 9.82 (br s, 1H), 8.09 (d, 1H, J = 8.2), 7.77 (dd, 1H, J = 7.7, 1.1), 7.60 (td, 1H, J = 7.7, 1.6), 7.34 (m, 4H), 7.26 (m, 2H), 2.68 (m, 3H), 2.26 (m, 1H); ^{13}C-NMR: δ 173.0, 161.9, 144.0, 136.3, 133.3, 128.7, 128.0, 127.6, 124.9, 124.8, 120.8, 120.7, 77.2, 34.7, 29.3; ms (30 eV): m/z 278 (M^+).

(±)-6,6a-Dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (8). This compound was prepared from 415 mg (2.50 mmoles) of **1**, 415 mg (2.50 mmoles) of methyl 2-formylbenzoate (**13**) [29], and 698 mg (12.5 mmoles) of iron powder in 8 mL of acetic acid using the procedure outlined for the preparation of **3a** with the reflux period extended to 8 h. Product **8** (415 mg, 72%) was isolated following flash chromatography on a 30 cm × 2 cm silica gel column eluted with 50% ether in hexanes containing 5% methanol, mp 255–258°C. IR: 3154, 1715, 1681,

1605 cm^{-1}; ^{1}H-NMR: δ 9.43 (br s, 1H), 8.30–7.55 (complex, 7H), 7.36 (br s, 1H), 6.25 (br s, 1H); ^{13}C-NMR: δ 164.1, 163.6, 140.7, 137.1, 133.5, 133.2, 131.1, 130.1, 128.1, 124.7, 124.1, 123.8, 119.9, 119.5, 67.0; ms (30 eV): *m/z* 250 (M^+). Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 72.00; H, 4.00; N, 11.20. Found: C, 72.03; H, 3.99; N, 11.15.

2,4(1*H*,3*H*)-Quinazolinedione (9). This compound was prepared from 415 mg (2.50 mmoles) of **1**, 495 mg (2.50 mmoles) of diphosgene (**14**), and 698 mg (12.5 mmoles) of iron powder in 8 mL of acetic acid using the procedure outlined for the preparation of **3a** with the reflux period extended to 8 h. Product **9** (348 mg, 86%) was isolated directly from the reaction mixture as a gray solid, mp 343–345°C (ref. 34; mp > 300°C). The spectral data matched those reported previously [34].

Representative procedure from 2-aminobenzamide: (±)-2,3-Dihydro-2-phenyl-4(1*H*)-quinazolinone (3a). A 100-mL three-necked round-bottomed flask, equipped with a reflux condenser, a magnetic stirrer and a nitrogen inlet, was charged with 7 mL of acetic acid, 250 mg (1.84 mmoles) of 2-aminobenzamide (**4**), and 195 mg (1.84 mmoles) of benzaldehyde (**2a**). The resulting solution was stirred at 23°C for 4 h or, alternatively, at 115°C for 30 min. The reaction mixture was cooled (if necessary), poured into saturated aqueous sodium chloride, and extracted with ether (1 × 50 mL) and ethyl acetate (1 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (two times) and saturated aqueous sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum and recrystallized from ethanol to give 370 mg (90%) of **3a** as a white solid. The mp and spectral data matched those reported above.

(±)-2,3-Dihydro-2-(4-methoxyphenyl)-4(1*H*)-quinazolinone (3b). This compound (420 mg, 90%) was prepared from 250 mg (1.84 mmoles) of **4** and 250 mg (1.84 mmoles) of **2b** in 7 mL of acetic acid. The mp and spectral data matched those reported above.

(±)-2-(2-Chlorophenyl)-2,3-dihydro-4(1*H*)-quinazolinone (3d). This compound (437 mg, 92%) was prepared from 250 mg (1.84 mmoles) of **4** and 258 mg (1.84 mmoles) of **2d** in 7 mL of acetic acid. The mp and spectral data matched those reported above.

(±)-Ethyl 4-(1,2,3,4-Tetrahydro-4-oxoquinazolin-2-yl)butanoate (3g). This compound (366 mg, 76%) was prepared from 250 mg (1.84 mmoles) of **4** and 265 mg (1.84 mmoles) of **2g** in 7 mL of acetic acid. The mp and spectral data matched those reported above.

2,3-Dihydro-2,2-dimethyl-4(1*H*)-quinazolinone (3i). This compound (297 mg, 92%) was prepared from 250 mg (1.84 mmoles) of **4** and 107 mg (1.84 mmoles) of **2i** in 7 mL of acetic acid. The mp and spectral data matched those reported above.

(±)-2,3-Dihydro-2-methyl-2-propyl-4(1*H*)-quinazolinone (3j). This compound (335 mg, 90%) was prepared from 250 mg (1.84 mmoles) of **4** and 158 mg (1.84 mmoles) of **2j** in 7 mL of acetic acid. The mp and spectral data matched those reported above.

(±)-2,3-Dihydro-2-methyl-2-(phenylmethyl)-4(1*H*)-quinazolinone (3l). This compound (408 mg, 88%) was prepared from 250 mg (1.84 mmoles) of **4** and 247 mg (1.84 mmoles) of **2l** in 7 mL of acetic acid. The mp and spectral data matched those reported above.

2,3-Dihydro-2,2-diphenyl-4(1*H*)-quinazolinone (3m). This compound (309 mg, 56%) was prepared from 250 mg (1.84 mmoles) of **4** and 335 mg (1.84 mmoles) of **2m** in 7 mL of acetic acid. The mp and spectral data matched those reported above.

Spiro[cyclohexane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3o). This compound (357 mg, 90%) was prepared from 250 mg (1.84 mmoles) of **4** and 180 mg (1.84 mmoles) of **2o** in 7 mL of acetic acid. The mp and spectral data matched those reported above.

(±)-Methyl 3-(1,2,3,4-Tetrahydro-2-methyl-4-oxoquinazolin-2-yl)propanoate (15). This compound was prepared by stirring 150 mg (1.10 mmoles) of **4** and 143 mg (1.10 mmoles) of **11** in 5 mL of acetic acid at 23°C for 24 h. Workup as above and recrystallization from methanol gave 192 mg (70%) of **15** as a white solid, mp 141–142°C. IR: 3287, 1722, 1655, 1615 cm^{-1}; ^{1}H-NMR: δ 7.85 (dd, 1H, *J* = 7.7, 1.6), 7.28 (ddd, 1 H, *J* = 8.2, 7.7, 1.6), 6.80 (t, 1H, *J* = 7.7), 6.62 (br s, 1H), 6.59 (d, 1H, *J* = 8.2), 4.22, (br s, 1H), 3.65 (s, 3H), 2.64 (dt, 1H, *J* = 17.0, 7.1), 2.52 (dt, 1H, *J* = 17.0, 7.1), 2.15 (dt, 1H, *J* = 14.0, 7.1), 2.06 (dt, 1H, *J* = 14.0, 7.1), 1.55, 2, 3H); ^{13}C-NMR δ 174.2, 164.5, 145.8, 134.0, 128.3, 118.6, 114.5, 114.0, 69.8, 51.9, 36.4, 29.0, 28.7; ms (30 eV): *m/z* 248 (M^+). Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.90; H, 6.45; N, 11.29. Found: C, 62.96; H, 6.46; N, 11.21. Treatment of equimolar amounts of **4** and **11** in 5 mL of acetic acid at 115°C for 8 gave **7a** in 75% yield. Additionally, heating **15** in acetic acid at 115°C for 8 h resulted in 98% conversion to **7a**. The mp and spectral data for **7a** matched those reported above.

Acknowledgments. B. N. thanks Oklahoma State University for a research assistantship and the Department of Chemistry for an O. C. Dermer Scholarship. Funding for the 300 MHz NMR spectrometer of the Oklahoma Statewide Shared NMR Facility was provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Finally, the authors wish to thank the OSU College of Arts and Sciences for funds to upgrade our departmental FT-IR and GC-MS instruments.

REFERENCES AND NOTES

[1] (a) Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. J Med Chem 1990, 33, 161; (b) Padia, J. K.; Field, M.; Hinton, J.; Meecham, K.; Pablo, J.; Pinnock, R.; Roth, B. D.; Singh, L.; Suman-Chauhan, N.; Trivedi, B. K.; Webdale, L. J Med Chem 1998, 41, 1042.

[2] (a) Hour, M.-J.; Huang, L.-J.; Kuo, S.-C.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K.-H. J Med Chem 2000, 43, 4479; (b) Chinigo, G. M.; Paige, M.; Grindrod, S.; Hamel, E.; Dakshanamurthy, S.; Chruszcz, M.; Minor, W.; Brown, M. L. J Med Chem 2008, 51, 4620.

[3] Ozaki, K.; Yamada, Y.; Oine, T.; Ishizuka, T.; Iwasawa, Y. J Med Chem 1985, 28, 568.

[4] Gouliaev, A. H.; Larsen, M.; Varming, T.; Mathiesen, C.; Johansen, T. H.; Scheel,-Kruger, J.; Olsen, G. M.; Nielsen, E. O. World Pat. WO 9942456, 1999; Chem Abstr 1999, 131, 184974.

[5] (a) Yale, H. L.; Kalkstein, M. J Med Chem 1967, 10, 334; (b) Alaimo, R. J.; Russell, H. E. J Med Chem 1972, 15, 335; (c) Wen, H.; Hao, W.; Gong, B. Zhongguo Kangshengsu Zazhi 2002, 27, 644; Chem Abstr 2004, 140, 399618.

[6] Gupta, R. C.; Nath, R.; Shanker, K.; Bhargava, K. P.; Kishor, K. J Ind Chem Soc 1979, 56, 219.

[7] (a) Orme, M. W.; Baindur, N.; Robbins, K. G.; Harris, S. M.; Kontoyianni, M.; Hurley, L. H.; Kerwin, S. M.; Mundy, G. R.; Petrie, C. Int. Pat. WO 9817267, 1998; Chem Abstr 1998, 128, 321662; (b) Petrie, C.; Orme, M. W.; Baindur, N.; Robbins, K. G.; Harris, S. M.; Kontoyianni, M.; Hurley, L. H.; Kerwin, S. M.; Mundy, G. R. Int. Pat. WO 9715308, 1998; Chem Abstr 1997, 127, 17703.

[8] (a) Biressi, M. G.; Cantrelli, G.; Carissimi, M.; Cattaneo, A.; Ravenna, F. Farmaco Ed Sci 1969, 24, 199; Chem Abstr 1969, 71, 61357; (b) Parish, H. A., Jr.; Gilliom, R. D.; Purcell, W. P.; Browne, R. K.; Spirk, R. F.; White, H. D. J Med Chem 1982, 25, 98.

[9] Bhalla, P. R.; Walworth, B. L., U.S. Pat. 4,431,440, 1984; Chem Abstr 1984, 100, 174857.

[10] Bunce, R. A.; Randall, M. H.; Applegate, K. G. Org Prep Proced Int 2002, 34, 493.

[11] Bunce, R. A.; Schammerhorn, J. E. J Heterocycl Chem 2006, 43, 1031.

[12] Bunce, R. A.; Nammalwar, B. J Heterocycl Chem 2009, 46, 172.

[13] Bunce, R. A.; Nammalwar, B. J Heterocycl Chem 2009, 46, 854.

[14] Shi, D.-Q.; Rong, L.-C.; Wang, J.-X.; Wang, X.-S.; Tu., S.-J.; Hu, H.-W. Gaodeng Xuexiao Huaxue Xuebao 2004, 25, 2051; Chem Abstr 2005, 153, 266896.

[15] Su, W.; Yang, B. Aust J Chem 2002, 55, 695.

[16] Cai, G.; Xu, X.; Li, Z.; Weber, W. P.; Lu, P. J Heterocycl Chem 2002, 39, 1271.

[17] Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. Tetrahedron Lett 2008, 49, 3814.

[18] Chen, J. X.; Wu, H. Y.; Su, W. K. Chin Chem Lett 2007, 18, 536; Chem Abstr 2008, 148, 517663.

[19] Qiao, R. Z.; Xu, B. L.; Wang, Y. H. Chin Chem Lett 2007, 18, 656; Chem Abstr 2008, 148, 517638.

[20] Salehi, P.; Dabiri, M.; Baghbanzadeh, M.; Bahramnejad, M. Synth Commun 2006, 36, 2287.

[21] Baghbanzedeh, M.; Salehi, P.; Dabiri, M.; Kozehgary, G. Synthesis 2006, 344.

[22] Surpur, M. P.; Singh, P. R.; Patil, S. B.; Samant, S. D. Synth Commun 2007, 37, 1965.

[23] Shaterian, H. R.; Oveisi, A. R.; Honarmand, M. Synth Commun 2010, 40, 1231.

[24] Shaabani, A.; Maleki, A.; Mofakham, H. Synth Commun 2008, 38, 3751.

[25] Although this paper was in review, a report detailing the synthesis of **6** and related compounds using a similar strategy appeared, see Wang, M.; Dou, G.; Shi, D. J Comb Chem 2010, 12, 582.

[26] Bordwell, F. G. Acc Chem Res 1988, 21, 456; The larger pKa of the aniline protons (30.6) *vs* benzamide (23.4) protons indicates that the aniline nitrogen is more basic and, therefore, more nucleophilic.

[27] It was well known that these conditions do not hydrogenolyze aromatic halides, see Mosley, W. L. J Org Chem 1959, 24, 421 and ref 10, but less was known about aliphatic halides such as **9**.

[28] Aeberli, P.; Houlihan, W. J Org Chem 1968, 33, 2402.

[29] Osuka, A.; Nakajima, S.; Maruyama, K. J Org Chem 1992, 57, 7355.

[30] Still, W. C.; Kahn, M.; Mitra, A. J Org Chem 1978, 43, 2923.

[31] Xu, G.; Micklatcher, M.; Silvestri, M. A.; Hartman, T. L.; Burrier, J.; Osterling, M. C.; Wargo, H.; Turpin, J. A.; Buckheit R. W., Jr.; Cushman, M. J Med Chem 2001, 44, 4092.

[32] Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. J Am Chem Soc 2009, 131, 11332.

[33] Larsen, S. D.; Connell, M. A.; Cudahy, M. M.; Evans, B. R.; May, P. D.; Meglasson, M. D.; O'Sullivan, T. J.; Schostarez, H. J.; Sih, J. C.; Stevens, F. C.; Tanis, S. P.; Tegley, C. M.; Tucker, J. A.; Vaillancourt, V. A.; Vidmar, T. J.; Watt, W.; Yu, J. H. J Med Chem 2001 44, 1217.

[34] Jiarong, L.; Xian, C.; Daxin, S.; Shuling, M.; Qing, L.; Qi, Z.; Jianhong, T. Org Lett 2009, 11, 1193.