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Stannous Chloride in Alcohol: A One-Pot Conversion of 2-Nitro-*N*-arylbenzamides to 2,3-Dihydro-1*H*-quinazoline-4-ones

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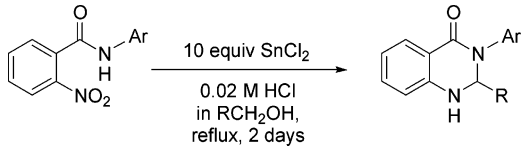

A novel one-step synthesis of 2,3-dihydro-1*H*-quinazolin-4-ones from 2-nitrobenzamides is reported. These reactions are mediated by stannous chloride in 0.02 M methanolic or ethanolic HCl solution and proceed in good yields.

Like other members of the quinazolinone family, 2,3-dihydro-1*H*-quinazolin-4-one (DHQ)[1] derivatives are established biologically and pharmaceutically important compounds.[2−4] The DHQ ring system can generally be prepared by the reaction of anthranilamides with aldehydes or ketones under either acidic or basic conditions,[5−8] and the typical preparation of anthranilamides, in turn, proceeds by the reaction of anilines with isatoic anhydride. However, this is not an effective protocol if the anilines are substituted with an electron-withdrawing group[9] or present either two *ortho* substituents or one bulky *ortho* substituent. In these cases, the aniline does not react with isatoic anhydride even at elevated temperatures.[10]

A recent report details the preparation of DHQ compounds by the reductive desulfurization of 2-thioxo-3*H*-quinazolin-4-ones with nickel boride in dry methanol,[11] but its usefulness is offset by the fact that the 2-thioxo-3*H*-quinazolin-4-one preparation is a multistep process as well as the fact that derivatization of the C2 position is limited by the nature of this reaction. A one-pot synthesis of DHQ by reductive cyclization of *o*-nitrobenzamides with aldehydes or ketones using $TiCl_4$/Zn in anhydrous THF has also been reported.[12] However, none of the DHQ compounds prepared by this method contained 3-aryl substituents with electron-withdrawing groups at the *ortho* position. Herein, we describe a new one-pot synthesis of DHQ derivatives accommodating 3-aryl substituents with *ortho* electron-withdrawing groups by treating the corresponding *o*-nitrobenzamides with stannous chloride in alcoholic 0.02 M HCl.

The genesis of this work was another project for which we needed a general procedure for the preparation of anthranilamides **3**, and our starting point was to evaluate the reaction of anilines (**2**) with isatoic anhydride (**1**). While this procedure worked nicely for many anilines, hindered and/or electron-deficient anilines such as 2-trifluoromethylaniline (**2a**) and 2,6-dichloroaniline (**2b**) delivered, at best, only a trace amount of the desired anthranilamide **3** (Scheme 1).

Clearly, these anilines have insufficient nucleophilicity; a literature report suggests that even *o*-chloroaniline (**2c**) is too deactivated (an 8% yield of **3c** was obtained).[6] To countermand this lack of reactivity, we decided to investigate the use of *o*-nitrobenzoyl chloride (**4**) in place of isatoic anhydride in hopes that its increased electrophilicity would induce nucleophilic attack by poor nucleophiles such as **2a**−**c**. Indeed, *o*-nitrobenzamides **5** were obtained in good yields by the reaction of these anilines **2** in refluxing chloroform solution. Having thus solved this reactivity problem and with *o*-nitrobenzamides **5** in hand, we turned our attention to nitro group reduction employing excess stannous chloride in methanol. Surprisingly, the major product of this reduction was not the anticipated anthranilamide **3**, but rather the heterocyclic DHQ product **6** (Scheme 2).

While we find no synthetic precedents for this interesting transformation, others have reported mechanistic studies in which it is claimed that autoxidation of stannous chloride subsequently induces oxidation of other molecular species including benzyl and allyl alcohols using atmospheric oxygen.[13−15] The authors of these papers explained their observations through a peroxide theory of autoxidation in which oxidations of these types are due to the formation of metastable peroxides.[13] In a similar study, alcohols, including methanol and ethanol, were oxidized in the presence of stannous chloride and base in aqueous solution.[16]

Our results, coupled with these previous studies, suggest that stannous chloride-mediated conversion of **5** to **6** in methanol proceeds via the generation of formaldehyde by methanol oxidation with subsequent

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(1) DHQ is for 2,3-dihydro-1*H*-quinazolin-4-one(s) throughout the paper.

(2) Bonola, G.; Da Re, P.; Magistretti, M. J.; Massarani, E.; Setnikar, I. *J. Med. Chem.* **1968**, *11*, 1136−1139.
(3) Levin, J. I.; Chan, P. S.; Bailey, T.; Katocs, A. S., Jr.; Venkatesan, A. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1141−1146.
(4) Okumura, K.; Oine, T.; Yamada, Y.; Hayashi, G.; Nakama, M. *J. Med. Chem.* **1968**, *11*, 348−352.
(5) Ozaki, K.; Yamada, Y.; Oine, T.; Ishizuka, T.; Iwasawa, Y. *J. Med. Chem.* **1985**, *28*, 568−576.
(6) Yale, H. L. *J. Heterocycl. Chem.* **1977**, *14*, 1357−1359.
(7) Kilroe Smith, T. A.; Stephen, H. *Tetrahedron* **1957**, *1*, 38−44.
(8) Feldman, J. R.; Wagner, E. C. *J. Org. Chem.* **1942**, *7*, 31−47.
(9) Tani, J.; Yamada, Y.; Oine, T.; Ochiai, T.; Ishida, R.; Inoue, I. *J. Med. Chem.* **1979**, *22*, 95−99.
(10) Coyne, W. E.; Cusic, J. W. *J. Med. Chem.* **1968**, *11*, 1208−1213.
(11) Khurana, J. M.; Kukreja, G. *J. Heterocycl. Chem.* **2003**, *40*, 677−679.
(12) Shi, D.; Rong, L.; Wang, J.; Zhuang, Q.; Wang, X.; Hu, H. *Tetrahedron Lett.* **2003**, *44*, 3199−3201.
(13) Haring, R. C.; Walton, J. H. *J. Phys. Chem.* **1933**, *37*, 133−145.
(14) Haring, R. C.; Walton, J. H. *J. Phys. Chem.* **1933**, *37*, 375−380.
(15) Haring, R. C.; Walton, J. H. *J. Phys. Chem.* **1934**, *38*, 153−160.
(16) Berentsveig, V. V.; Barinova, T. V.; Rudenko, A. P. *React. Kinet. Catal. Lett.* **1979**, *10*, 333−336.

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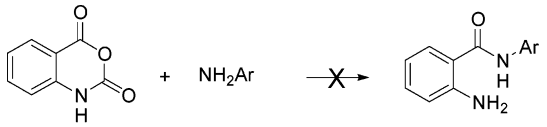
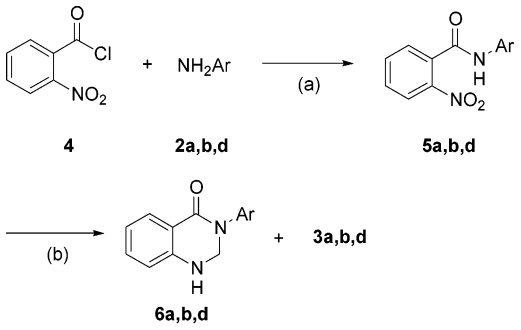
SCHEME 1



1 **2a-c** **3a-c**

a: Ar = 2,6-$(Cl)_2C_6H_3$; **b**: Ar = 2-$CF_3C_6H_4$; c: Ar = 2-ClC_6H_4

SCHEME 2. Synthesis of 6[a]

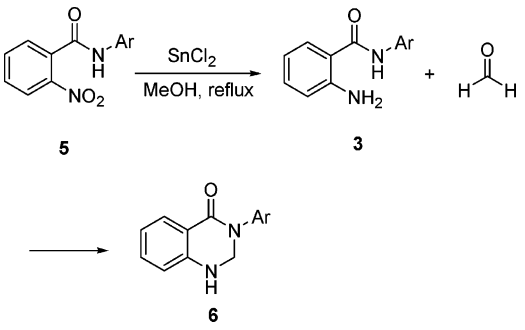


4 **2a,b,d** **5a,b,d** **6a,b,d**

a: Ar = 2,6-$(Cl)_2C_6H_3$; **b**: Ar = 2-$CF_3C_6H_4$; **d**: Ar = C_6H_5

[a] Reagents and conditions: (a) $CHCl_3$, reflux, 3 h, 80−85%; (b) 10 equiv of $SnCl_2$, MeOH, reflux, 2 days, 29−40% of **6a**−**c**.

SCHEME 3



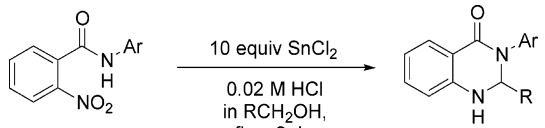
5 **3** **6**

anthranilamide condensation (Scheme 3). While the major products of these nitro reduction reactions were DHQ, the yields of **6** were between 29% and 47% and the anthranilamides (**3**) were observed but in only trace amounts.

Literature reports indicated that the autoxidation rate of stannous chloride increases linearly with increasing concentrations of hydrochloric acid in alcohol[15] as well as with increasing temperature − presumably due to the greater solubility of oxygen at elevated temperature.[13] Armed with these observations, we set out to optimize the conditions for **3** → **6** by varying the concentration of HCl in the alcohol solution while setting the temperature at reflux. Initially 0.5 M HCl solutions of methanol and ethanol were employed together with 5−30 equiv of stannous chloride. However, reaction yields of **6** dropped to below 10%. After various trials in which the concentration of HCl was decreased, we concluded optimal conditions are 0.02 M HCl solutions together with stannous chloride (10 equiv) at reflux (Scheme 4). As illustrated in Table 1, these conditions produced yields ranging from 50% to 73%.

Attempts to employ benzyl alcohol as solvent/reactant, both with and without HCl, produced complicated reaction mixtures. In addition, the reaction workup was

SCHEME 4



5 **6**

TABLE 1. Synthesis of 6 (10 equiv of $SnCl_2$, 0.02 M HCl, RCH_2OH)

entry	product	R	Ar	yield (%)[a]
1	**6a**	H	2,6-$(Cl)_2C_6H_3$	59
2	**6b**	H	2-$CF_3C_6H_4$	63
3	**6d**	H	C_6H_5	62
4	**6e**	CH_3	2,6-$(Cl)_2C_6H_3$	73
5	**6f**	CH_3	2-$CF_3C_6H_4$	64
6	**6g**	CH_3	C_6H_5	50

[a] 2-Amino-*N*-arylbenzamide **3** was isolated in ∼20−30% yield in each case.

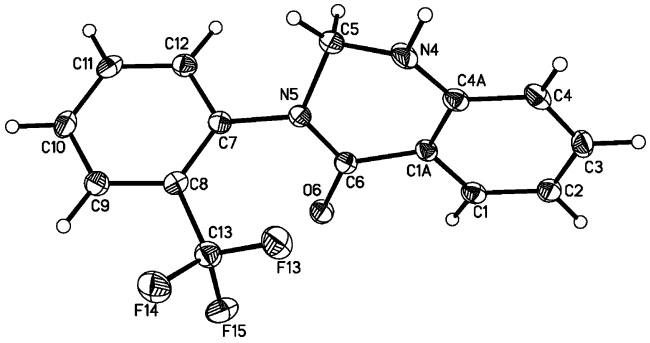


FIGURE 1. ORTEP diagram of **6b**.

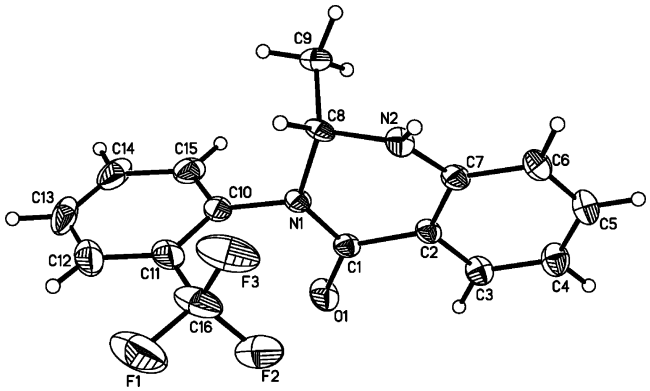


FIGURE 2. ORTEP diagram of **6f**.

difficult due to the high boiling point of benzyl alcohol. Finally, the structures of **6a**,**b**,**d**−**g** were confirmed by IR, ^1H NMR, and ^{13}C NMR. The structures of **6b** and **6f** were further confirmed by X-ray analysis (Figures 1 and 2).

In summary, we have discovered a novel one-pot conversion of *o*-nitrobenzamides to DHQs by the action of stannous chloride in methanolic or ethanolic 0.02 M HCl solution under atmospheric oxygen. On the basis of related mechanistic work, this reaction appears to proceed by autoxidation of stannous chloride, which produces peroxides, the species that ultimately oxidizes the alcohol.

Experimental Section

***N*-(2,6-Dichlorophenyl)-2-nitrobenzamide (5a).** 2-Nitrobenzoyl chloride **4** (1 g, 5.4 mmol) in $CHCl_3$ was treated with 2,6-dichloroaniline **2a** (3.5 g, 21.6 mmol) under a nitrogen atmosphere at reflux for 3 h. Upon cooling, the reaction mixture was diluted with $CHCl_3$ and washed consecutively with aq 1 M HCl and saturated aq $NaHCO_3$. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Crystallization of the residue in $CHCl_3$ gave **5a** (1.4 g, 84%) as white needles: mp 223−224 °C; IR (neat) 3226, 1665, 1616, 1520, 1352 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, J = 8 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 7.51 (dd, J = 8 Hz, 1H), 7.66 (dd, J = 8 Hz, 1H), 7.43 (d, J = 8 Hz, 2H), 7.36 (br s, 1H), 7.25 (d, J = 8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 164.7, 147.8, 134.6, 134.4, 132.7, 132.1, 130.3, 129.9, 129.3, 125.0.

2-Nitro-*N*-(2-trifluoromethylphenyl)benzamide (5b). Following the procedure described for **5a**, **4** and **2b** gave **5b**: white needles in 85% yield; mp 179−180 °C; IR (neat) 3219, 1650, 1610, 1522, 1351 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, J = 8 Hz, 1H), 8.17 (d, J = 8 Hz, 1H), 7.76 (dd, J = 8 Hz, 8 Hz, 1H), 7.72−7.62 (m, 5H), 7.34 (dd, J = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.3, 147.1, 135.4, 134.9, 133.9, 133, 131.7, 130.8, 129.6, 128.1, 127.1 (q, J = 4.5 Hz), 126.3 (q, 30 Hz), 125.0, 124.2 (q, 272 Hz).

2-Nitro-*N*-phenylbenzamide (5d). Following the procedure described for **5a**, **4** and **2d** gave **5d**: yellow solid in 80% yield; mp 152−153 °C; IR (neat) 3249, 1656, 1600, 1527, 1342 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, J = 8 Hz, 1H), 7.72−7.54 (m, 6H), 7.35 (dd, J = 7.2 Hz, 2H), 7.17 (dd, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 146.5, 137.5, 134.1, 133.1, 131.0, 129.4, 128.8, 125.4, 124.9, 120.7.

3-(2,6-Dichlorophenyl)-2,3-dihydro-1*H*-quinazolin-4-one (6a). $SnCl_2{\cdot}2H_2O$ (1.1 g, 5 mmol) and **5a** (155 mg, 0.5 mmol) were dissolved in 0.02 M methanolic HCl solution and refluxed for 2 d under atmospheric oxygen. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate, and washed with aq $NaHCO_3$ and water. The organic layer was dried over anhydrous sodium sulfate, concentrated, and the residue was purified by column chromatography (30% EtOAc in *n*-hexane) to give **6a** (86 mg, 59%) as a white solid: mp 155−157 °C; IR (neat) 3351, 1644, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.01 (d, J = 8 Hz, 1H), 7.39 (d, J = 8 Hz, 2H), 7.34 (dd, J = 8 Hz, 1H), 7.21 (dd, J = 8 Hz, 1H), 6.93 (dd, J = 8 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 4.83 (s, 1H), 4.53 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.5, 148.1, 136.4, 135.3, 134.0, 129.9, 129.5, 128.0, 120.4, 117.8, 116.3, 61.0.

3-(2-Trifluoromethylphenyl)-2,3-dihydro-1*H*-quinazolin-4-one (6b). Following the procedure described for **6a**, **5b** gave **6b**: white solid in 63% yield; mp 169−171 °C; IR (neat) 3341, 1672, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, J = 8 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 7.63 (dd, J = 8 Hz, 1H), 7.48 (dd, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.35 (dd, J = 8 Hz, 1H), 6.93 (dd, J = 8 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 4.89 (d, J = 10 Hz, 1H), 4.69 (d, J = 10 Hz, 1H), 4.64−4.36 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.4, 147.9, 139.1, 133.9, 133.6, 131.2, 130.7, 129.5, 128.8, 128.5 (q, 38 Hz), 127.6 (q, 4.6 Hz), 123.6 (q, 270 Hz), 120.5, 118.1, 116.3, 62.8.

3-Phenyl-2,3-dihydro-1*H*-quinazolin-4-one (6d). Following the procedure described for **6a**, **5d** gave **6d**: white solid in 62% yield; mp 173−174 °C; IR (neat) 3292, 1645, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, J = 8 Hz, 1H), 7.45−7.20 (m, 6H), 6.93 (dd, J = 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 4.95 (s, 2H), 4.6−3.6 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 147.8, 141.2, 133.8, 129.6, 129.3, 126.7, 125.3, 120.3, 118.4, 115.6, 62.3.

3-(2,6-Dichlorophenyl)-2-methyl-2,3-dihydro-1*H*-quinazolin-4-one (6e). Following the procedure described for **6a**, **5a** gave **6e**: white solid in 73% yield; mp 184−186 °C; IR (neat) 3315, 1639, 1606 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, J = 8 Hz, 1H), 7.46−7.36 (m, 2H), 7.32 (dd, J = 8 Hz, 1H), 7.24 (dd, J = 8 Hz, 1H), 6.89 (dd, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H), 5.39 (q, J = 6 Hz, 1H), 4.8−4.6 (br s, 1H), 1.28 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.0, 147.6, 136.8, 135.8, 135.4, 134.0, 129.9, 129.5, 129.0, 128.8, 119.9, 116.8, 115.7, 66.8, 19.7.

2-Methyl-3-(2-trifluoromethylphenyl)-2,3-dihydro-1*H*-quinazolin-4-one (6f). Following the procedure described for **6a**, **5b** gave **6f**: white solid in 64% yield; mp 195−196 °C; IR (neat) 3318, 1634, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99−7.93 (m, 1H), 7.79−7.75 (m, 1H), 7.63 (dd, J = 8 Hz, 1H), 7.54−7.44 (m, 1H), 7.41 (d, J = 8 Hz, 1H), 7.37−7.30 (m, 1H), 6.94−6.86 (m, 1H), 6.74−6.70 (m, 1H), 5.35 (q, J = 6 Hz, 0.3 × 1H), 5.09 (q, J = 6 Hz, 0.7 × 1H), 4.6−4.4 (br s, 1H), 1.41 (d, J = 6 Hz, 0.7 × 3H), 1.23 (d, J = 6 Hz, 0.3 × 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 147.4, 146.2, 137.9, 135.2, 134.0, 133.3, 133.1, 131.2, 130.6, 129.7, 129.3, 128.8, 128.6, 127.8, 127.7, 127.6, 124.9, 122.2, 120.1, 119.9, 117.2, 116.9, 116.0, 115.5, 68.2, 67.7, 20.6, 19.8.

2-Methyl-3-phenyl-2,3-dihydro-1*H*-quinazolin-4-one (6g). Following the procedure described for **6a**, **5d** gave **6g**: white solid in 50% yield; mp 167−169 °C; IR (neat) 3295, 1632, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, J = 8 Hz, 1H), 7.41 (dd, J = 8 Hz, 2H), 7.34−7.28 (m, 4H), 6.87 (dd, J = 7 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 5.20 (q, J = 6 Hz, 1H), 4.7−4.5 (br s, 1H), 1.39 (d, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.1, 146.2, 140.4, 133.9, 129.5, 129.3, 128.0, 127.5, 119.6, 116.8, 115.3, 68.7, 21.1.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of compounds **5a**,**b**,**d** and **6a**,**b**,**d**−**g**; crystallographic data for compounds **6b** and **6f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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