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FACILE AND EFFICIENT SYNTHESIS OF 2-AMINOQUINOLINE DERIVATIVES REDUCED BY Zn/AcOH

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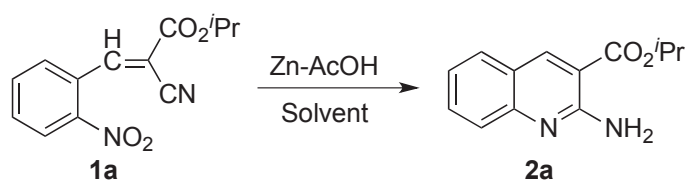
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Abstract – In this paper, a simple and efficient method for one-pot synthesis of 2-aminoquinolines was accomplished in good yields via reductive cyclization of nitro and cyano groups mediated by zinc/acetic acid is reported.

Nitrogen-containing heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products. Quinoline derivatives occur in a large number of natural products¹ and drug-like compounds.² 2-Aminoquinoline derivatives are especially important because of their pharmaceutical activities and applications, including antiprotozoals,³ antidepressants,⁴ antihypertensives,⁵ anti-HIV,⁶ anti-Alzheimer disease,⁷ melanin-concentrating hormone receptor antagonists⁸ and Src kinase inhibitors.⁹

There has been a large amount of effort devoted to developing efficient methods for the preparation of substituted 2-aminoquinolines. Srinivasan *et al.*¹⁰ reported the synthesis of 2-aminoquinoline-3-carbonitrile from the reaction of arylidenemalononitriles with enaminone. Wilson *et al.*¹¹ described the synthesis of 2-aminoquinolines using microwave-assisted synthesis. Basic condensations of aromatic ketones with (dimethylamino)propionitrile,¹² Frielander's approach¹³ and nucleophilic substitution of chloroquinoline¹⁴ have also been used to synthesize 2-aminoquinolines. However, these methods have disadvantages such as forcing conditions, unsatisfactory yields, long reaction times, high temperatures, complex manipulations, and commercially unavailable starting materials. Zhou *et al.*^{15,16} obtained 2-aminoquinoline-3-carboxylic acid derivatives rapidly in good yields by treating nitrocyano olefins with a low-valent titanium reagent in dry THF at room temperature. The same group also reported the intramolecular reductive coupling of cyano and nitro groups induced by

SmI₂ to produce 2-aminoquinoline in good yields.¹⁷ However, the requirement of anhydrous and/or anaerobic conditions detracts from the usefulness of these methods. Coupling between cyano and nitro groups can also be achieved using tin dichloride,¹⁸ however, the reaction time is long, involving heating under reflux for 6 h. Reductive coupling of cyano and nitro groups can be achieved using iron and acetic acid, but yields are generally moderate.¹⁹⁻²¹ Therefore, more efficient methods to prepare these kinds of compounds with mild reaction conditions and high yields are desirable. The zinc-acetic acid (Zn/AcOH) couple is a well-known reducing reagent, capable of a wide range of reactions,^{22,23} among which reductions of nitro, carbonyl and activated alkenes are the most common. We found that 2-amino-3-cyanoquinoline can be obtained by Zn/AcOH-mediated cyano–nitrile coupling in a study optimizing the synthesis of substituted quinoline-1-oxides.²⁴ In this study, we further explore the potential of Zn/AcOH-mediated cyano–nitrile coupling and describe a convenient one-pot reductive cyclization protocol for the synthesis of 2-aminoquinolines.



Scheme 1

Table 1. Conditions trialed to optimize for the reductive cyclization reduction

Entry	Temperature (°C)	Ratio ^a	Solvent	Yield (%) ^b
1	60	1:1	EtOH	39
2	60	1:2	EtOH	57
3	60	1:3	EtOH	72
4	60	1:4	EtOH	83
5	60	1:5	EtOH	75
6	rt	1:4	EtOH	33
7	40	1:4	EtOH	60
8	reflux	1:4	EtOH	86
9	reflux	1:4	THF	67
10	reflux	1:4	MeCN	53
11	reflux	1:4	CHCl ₃	57

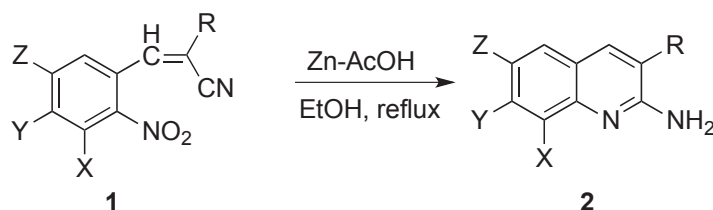
^aRatio of **1a** and the zinc

^bIsolated yield after recrystallization of the product

Isopropyl-2-cyano-3-(2-nitrophenyl)acrylate (**1a**) was used as a model substrate to optimize the experimental conditions for the proposed reductive cyclization reaction (Scheme 1). The results are summarized in Table 1.

The ratio of **1a** to Zn/AcOH was evaluated between the range of 1:1 and 1:5. The yield of 2-aminoquinoline **2a** increased as the ratio of **1a** to Zn/AcOH was increased from 1:1 to 1:4 (Table 1, entries 1–4). Further increasing this ratio to 1:5 resulted in a decrease in yield compared with that obtained using a ratio of 1:4 (Table 1, entry 5). Therefore, 1:4 was chosen for all further reactions. Reaction temperature was investigated next; heating to reflux resulted in the highest yield (Table 1, entries 6–8). Solvent screening revealed that EtOH was preferable to the other solvents tested (Table 1, entries 8–11). We concluded that the optimal conditions are 4 equivalents of Zn/AcOH in EtOH heated at reflux.

With the optimized conditions in hand, we then examined the applicability of the process for the synthesis of other 2-aminoquinolines (Scheme 2).



Scheme 2

Table 2. Synthesis of 2-aminoquinolines by Zn/AcOH reduction

Entry	X	Y	Z	R	Product	Yield (%) ^a
1	H	H	H	CO ₂ ⁱ Pr	2a	86
2	H	H	H	CO ₂ Me	2b	82
3	H	H	H	4-ClC ₆ H ₄	2c	79
4	H	H	H	CO ₂ Et	2d	87
5	H	H	Cl	CO ₂ Me	2e	90
6	H	H	Cl	CO ₂ Et	2f	83
7	H	H	Cl	CO ₂ ⁱ Pr	2g	82
8	H	OMe	OMe	C ₆ H ₅	2h	84
9	H	OCH ₂ O		4-BrC ₆ H ₄	2i	80
10	H	OCH ₂ O		C ₆ H ₅	2j	86

^aIsolated yield after recrystallization of the product

We found that the method was applicable to a broad selection of substrates (Table 2), with a range of groups in the R position tolerated including esters and substituted phenyls. Good or acceptable yields were obtained when a 5-Cl-, 4,5-OCH₂O- or 4,5-dimethoxy-substituted phenyl ring was present (entries 5–10). All the products were characterized by IR, HRMS and ¹H NMR spectroscopy.

In summary, a series of 2-aminoquinolines were synthesized by Zn/AcOH reaction of nitro and cyano groups. This protocol is advantageous compared with other published methods because it uses readily accessible materials, requires simple manipulations, and allows facile isolation of products via simple recrystallization.

EXPERIMENTAL

Commercial solvents and reagents were used as received. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm⁻¹. ¹H NMR was determined on Varian-300 MHz spectrometer in DMSO-*d*₆ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. MS data were obtained using microma GCT-TOF instrument (EI⁺). The synthesis of the reactant **1** is according to the report literature.²⁵

General procedure for the synthesis of **2** is represented as follows.

To a solution of 3-(2-nitrophenyl)acrylonitriles **1** (1 mmol) and Zn (4 mmol) in 5 mL of EtOH was added 0.2 mL AcOH, then the mixture was stirred at reflux for 1-2 h. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 30 mL of water and extracted with CHCl₃ (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and dried over anhydrous Na₂SO₄. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% EtOH.

Isopropyl 2-aminoquinoline-3-carboxylate (2a): white solid, mp 156-158 °C. IR (KBr) ν : 3417, 3146, 2831, 1669, 1611, 1515, 1446, 1409, 1267, 1163, 986, 828, 715, 688 cm⁻¹. ¹H NMR (300 MHz, DMSO-*d*₆) (δ , ppm): 1.36 (6H, d, *J* = 6.0 Hz, 2×CH₃), 5.18 (1H, m, OCH), 7.19 (3H, br s, NH₂+ ArH), 7.48 (1H, d, *J* = 8.4 Hz, ArH), 7.61 (1H, t, *J* = 7.8 Hz, ArH) 7.84 (1H, d, *J* = 8.1 Hz, ArH), 8.71 (1H, s, ArH). HRMS [Found: *m/z* 230.1058 (M⁺), calcd for C₁₃H₁₄N₂O₂: M, 230.1055]. Anal. Calcd for C₁₃H₁₄N₂O₂: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.71; H, 6.29; N, 12.28%.

Methyl 2-aminoquinoline-3-carboxylate (2b): white solid, mp 120-122 °C. IR (KBr) ν : 3427, 3157, 2956, 1701, 1631, 1565, 1437, 1291, 1203, 1132, 1078, 954, 800, 748, 597 cm⁻¹. ¹H NMR (300 MHz, DMSO-*d*₆) (δ , ppm): 3.88 (3H, s, OCH₃), 7.19 (3H, br s, NH₂+ ArH), 7.48 (1H, s, ArH), 7.62 (1H, s, ArH), 7.83 (1H, s, ArH), 8.75 (1H, s, ArH). HRMS [Found: *m/z* 202.0743 (M⁺), calcd for C₁₁H₁₀N₂O₂: M, 202.0742]. Anal. Calcd for C₁₁H₁₀N₂O₂: C, 65.34; H, 4.98. N, 13.85; Found: C, 65.45; H, 4.87; N, 13.97%.

3-(4-Chlorophenyl)quinolin-2-amine (2c): white solid, mp 206-208 °C. IR (KBr) ν : 3438, 3126, 2757, 1643, 1568, 1496, 1434, 1200, 1126, 1089, 1016, 906, 838, 755, 688 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6) (δ , ppm): 6.09 (2H, s, NH₂), 7.18 (1H, m, ArH), 7.51 (5H, m, ArH), 7.68 (2H, d, $J = 7.8$ Hz, ArH), 7.82 (1H, s, ArH). HRMS [Found: m/z 254.0612 (M^+), calcd for C₁₅H₁₁N₂³⁵Cl: M, 254.0611]. Anal. Calcd for C₁₅H₁₁ClN₂: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.61; H, 4.48; N, 11.15%.

Ethyl 2-aminoquinoline-3-carboxylate (2d): white solid, mp 124-126 °C. IR (KBr) ν : 3418, 3275, 3148, 2979, 1697, 1626, 1566, 1482, 1439, 1290, 1204, 1137, 1083, 1015, 960, 802, 750 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6) (δ , ppm): 1.34 (3H, t, $J = 4.2$ Hz, CH₃), 4.34 (2H, m, OCH₂), 7.19 (3H, br s, NH₂+ ArH), 7.48 (1H, d, $J = 8.1$ Hz, ArH), 7.61 (1H, t, $J = 6.0$ Hz, ArH), 7.83 (1H, d, $J = 7.2$ Hz, ArH), 8.73 (1H, s, ArH). HRMS [Found: m/z 216.0901 (M^+), calcd for C₁₂H₁₂N₂O₂: M, 216.0899]. Anal. Calcd for C₁₂H₁₂N₂O₂: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.78; H, 5.45; N, 12.84%.

Methyl 2-amino-6-chloroquinoline-3-carboxylate (2e): white solid, mp 184-186 °C. IR (KBr) ν : 3427, 3268, 3127, 2900, 1705, 1628, 1561, 1483, 1440, 1362, 1273, 1185, 1082, 930, 822, 792, 667 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6) (δ , ppm): 3.88 (3H, s, OCH₃), 7.30 (2H, s, NH₂), 7.47 (1H, d, $J = 8.7$ Hz, ArH), 7.60 (1H, d, $J = 7.8$ Hz, ArH), 7.97 (1H, s, ArH), 8.75 (1H, s, ArH). HRMS [Found: m/z 236.0351 (M^+), calcd for C₁₁H₉N₂O₂³⁵Cl: M, 236.0353]. Anal. Calcd for C₁₁H₉ClN₂O₂: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.96; H, 3.71; N, 11.72%.

Ethyl 2-amino-6-chloroquinoline-3-carboxylate (2f): white solid, mp 186-188 °C. IR (KBr) ν : 3422, 3274, 3141, 2993, 1701, 1633, 1563, 1490, 1360, 1277, 1191, 1086, 963, 827, 798, 696, 668 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6) (δ , ppm): 1.34 (3H, t, $J = 7.2$ Hz, CH₃), 4.34 (2H, m, OCH₂), 7.32 (2H, s, NH₂), 7.46 (1H, d, $J = 9.0$ Hz, ArH), 7.59 (1H, dd, $J_1 = 2.1$ Hz, $J_2 = 9.0$ Hz, ArH), 7.98 (1H, s, ArH), 8.74 (1H, s, ArH). HRMS [Found: m/z 250.0508 (M^+), calcd for C₁₂H₁₁N₂O₂³⁵Cl: M, 250.0509]. Anal. Calcd for C₁₂H₁₁ClN₂O₂: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.60; H, 4.37; N, 11.31%.

Isopropyl 2-amino-6-chloroquinoline-3-carboxylate (2g): white solid, mp 206-208 °C. IR (KBr) ν : 3423, 3274, 3149, 2974, 1700, 1636, 1560, 1486, 1412, 1276, 1238, 1190, 1070, 820, 799, 668 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6) (δ , ppm): 1.34 (6H, d, $J = 6.0$ Hz, 2×CH₃), 5.16 (1H, m, OCH), 7.32 (2H, s, NH₂), 7.47 (1H, d, $J = 9.0$ Hz, ArH), 7.60 (1H, dd, $J_1 = 2.4$ Hz, $J_2 = 9.0$ Hz, ArH), 7.99 (1H, d, $J = 2.1$ Hz, ArH), 8.72 (1H, s, ArH). HRMS [Found: m/z 264.0663 (M^+), calcd for C₁₃H₁₃N₂O₂³⁵Cl: M, 264.0666]. Anal. Calcd for C₁₃H₁₃ClN₂O₂: C, 58.99; H, 4.95; N, 10.58. Found: C, 58.89; H, 5.06; N, 10.69%.

6,7-Dimethoxy-3-phenylquinolin-2-amine (2h): white solid, mp 204-206 °C. IR (KBr) ν : 3451, 3294, 3164, 2999, 1637, 1624, 1500, 1460, 1395, 1247, 1166, 1013, 849, 785, 755, 610 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6) (δ , ppm): 3.79 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 5.61 (2H, s, NH₂), 6.94 (1H, s, ArH), 7.13 (1H, s, ArH), 7.40 (1H, s, ArH), 7.48 (4H, d, $J = 3.6$ Hz, ArH), 7.69 (1H, s, ArH). HRMS [Found: m/z 280.1209 (M^+), calcd for C₁₇H₁₆N₂O₂: M, 280.1212]. Anal. Calcd for C₁₇H₁₆N₂O₂: C, 72.84; H, 5.75;

N, 9.99. Found: C, 72.72; H, 5.88; N, 9.87%.

7-(4-Bromophenyl)-[1,3]dioxolo[4,5-g]quinolin-6-amine (2i): brown solid, mp 192-194 °C. IR (KBr) ν : 3477, 3457, 3161, 2923, 1630, 1602, 1490, 1410, 1226, 1034, 937, 829, 744, 589 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6) (δ , ppm): 6.11 (2H, s, OCH₂O), 6.31 (2H, s, NH₂), 7.00 (1H, s, ArH), 7.19 (1H, s, ArH), 7.44 (2H, d, $J = 7.5$ Hz, ArH), 7.68 (2H, d, $J = 7.5$ Hz, ArH), 7.80 (1H, s, ArH). HRMS [Found: m/z 342.0003 (M^+), calcd for C₁₆H₁₁N₂O₂⁷⁹Br: M, 342.0004]. Anal. Calcd for C₁₆H₁₁BrN₂O₂: C, 56.00; H, 3.23; N, 8.16. Found: C, 56.12; H, 3.11; N, 8.27%.

7-Phenyl-[1,3]dioxolo[4,5-g]quinolin-6-amine (2j): white solid, mp 114-116 °C. IR (KBr) ν : 3445, 3299, 3151, 2892, 1632, 1602, 1485, 1410, 1231, 1122, 1040, 946, 836, 779, 701, 587 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6) (δ , ppm): 5.71 (2H, s, NH₂), 6.06 (2H, s, OCH₂O), 6.92 (1H, s, ArH), 7.12 (1H, s, ArH), 7.45 (5H, m, ArH), 7.68 (1H, s, ArH). HRMS [Found: m/z 264.0898 (M^+), calcd for C₁₆H₁₂N₂O₂: M, 264.0899]. Anal. Calcd for C₁₆H₁₂N₂O₂: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.84; H, 4.44; N, 10.69%.

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