J. Chem. Research (S), 1998, 398–399†

Facile and Efficient Synthesis of 2-Aminoquinoline-3-carboxylic Acid Derivatives *via* Reductive Cyclization of Nitro and Cyano Groups Induced by Low-valent Titanium†

Longhu Zhou,* Sujiang Tu, Daqin Shi and Guiyuan Dai

Department of Chemistry, Xuzhou Normal University, Xuzhou, 221009, P.R. China

A short and facile synthesis of a series of 2-aminoquinoline-3-carboxylic acid derivatives was accomplished in good yields *via* the intramolecular reductive cyclization of nitrocyano olefins promoted by $TiCl_4/Zn$.

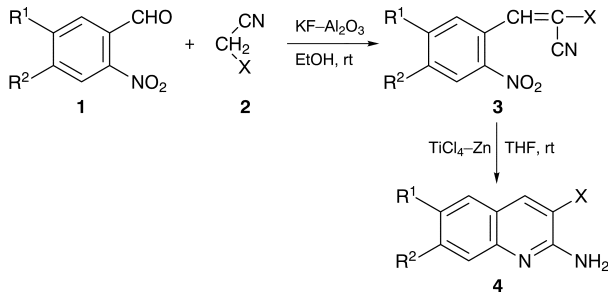
Low-valent titanium reagents have an exceedingly high ability to promote reductive coupling of carbonyl compounds and are attracting increasing interest in organic synthesis. Many other functional groups can also be coupled.[1] Recently, we reported the cyclodimerization of α,β-unsaturated ketones and α,β-unsaturated nitrile compounds promoted by this reagent, yield functional cyclopentanes[2] and cyclopentenes[3] respectively.

2-Aminoquinoline derivatives have attracted much concern due to their biological properties.[4] For instance, simple molecules such as 2-aminoquinoline have been isolated from a North American mushroom known for its antibacterial and antihelminthic activity.[5] It has been reported that 2-aminoquinoline analogues have antiprotozal,[6] antidepressent[7] and antihypertensive[8] properties. Recently, there has been considerable interest in the development of methodology for accessing these compounds. In most reported methods for the synthesis of 2-aminoquinoline derivatives strong basic solvents as well as harsh thermal conditions are employed, *e.g.* basic condensations of aromatic ketones with (dimethylamino)propionitrile,[9a,b] Frielander's approach[9c] and nucleophilic substitution on the previously formed chloroquinoline under strong basic conditions.[9d]

The cyano group is relatively more stable to low-valent titanium reagents than carbonyl and cannot be reduced unless the reaction mixture is refluxed for a long time, and giving only low yield.[10] The nitro group, however, is relatively more easily reduced.[11] We considered that the intermediate derived from a more active functional group by treatment with low-valent titanium could perhaps attack a more stable functional group which otherwise would not react with low-valent titanium. Therefore, we have studied the behaviour of a molecule containing both cyano and nitro groups, **3**, when treated with titanium(IV) chloride and zinc in tetrahydrofuran at room temperature.

As expected, 2-aminoquinoline-3-carboxylic acid derivatives **4** were rapidly obtained in good yields by treatment of nitrocyano olefins **3** with $TiCl_4$–Zn in dry THF at room temperature (Scheme 1). Our synthetic strategy was based on the use of $KF–Al_2O_3$ as catalyst for preparing key intermediates **3** from readily available starting materials and use of low-valent titanium to promote reductive cyclization of nitrocyano olefins **3** to produce products **4** under mild conditions.

Table 1 summarizes the results. All reactions could be carried out under mild conditions. However, treating aminocyano olefins derived from nitrocyano olefins **3** under the same reaction conditions gave no reaction.



Scheme 1

In conclusion, with its high yields, mild conditions as well as straightforward procedure, we think that the present method may be useful for the preparation of 2-aminoquinoline-3-carboxylic acid derivatives. Further studies to develop other new uses of this reagent are now in progress.

Experimental

Melting points were uncorrected. ^1H NMR spectra were obtained for solutions in $CDCl_3$ with Me_4Si as internal standard using a Bruker AC-80 spectrometer, mass spectra on a ZAB-HS or Finnigan MAT GC-MS spectrometer. Microanalyses were carried out using a Perkin-Elmer 240C analyser. IR spectra were recorded on a FTIR-8101 spectrometer in KBr.

General Procedure for Synthesis of Nitrocyano Olefins **3**.—Aromatic aldehyde (10 mmol), ethyl cyanoacetate or malononitrile (10 mmol), $KF–Al_2O_3$[12] (200 mg) and dry ethanol (5 cm^3) were added to a dry flask. The mixture was allowed to react at 30 °C during 2–3 h. On completion of the reaction the mixture was poured into water (50 cm^3) and extracted with diethyl ether (3 × 30 ml). The combined extracts were washed with water (2 × 20 ml, dried (Na_2SO_4) and the solvent was removed to give the crude product, which was further purified by recrystallization from ethanol.

3a: light tan needles, mp 139–140 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2250 (CN); δ_H 7.61–7.70 (3 H, m, ArH), 8.31–8.40 (1 H, m, ArH), 8.47 (1 H, s, —CH═) (Found: C, 60.2; H, 2.4; N, 14.3. $C_{10}H_5N_3O_2$ requires C, 60.3; H, 2.5; N, 14.1%).

3b: orange needles, mp 138–140 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2240 (CN), 1735 (CO); δ_H 3.98 (3 H, s, CH_3), 7.72–7.89 (3 H, m, ArH), 8.23–8.27 (1 H, m, ArH), 8.74 (1 H, s, —CH═) (Found: C, 57.0; H, 3.4; N, 12.2. $C_{11}H_8N_2O_4$ requires C, 56.9; H, 3.5; N, 12.1%).

Table 1 Yields of the products

Entry	R^1, R^2	X	Yield of **3** (%)	Yield of **4** (%)
a	H, H	CN	95	81
b	H, H	CO_2CH_3	91	91
c	H, H	$CO_2C_2H_5$	88	89
d	H, H	$CO_2C_3H_7$-*i*	79	85
e	H, H	$CO_2C_4H_9$-*n*	86	87
f	OCH_2O	CN	96	78
g	OCH_2O	CO_2CH_3	93	85
h	OCH_2O	$CO_2C_2H_5$	91	90
i	OCH_2	$CO_2C_3H_7$-*i*	84	79
j	OCH_2O	$CO_2C_4H_9$-*n*	90	86

---

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

3c: orange needles, mp 102–103 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2230 (CN), 1735 (CO); δ_H 1.40 (3 H, t, $J = 7.1$, CH_3), 4.42 (2 H, q, $J = 7.1$ Hz, OCH_2), 7.64–8.28 (4 H, m, ArH), 8.71 (1 H, s, CH═) (Found: C, 58.4; H, 4.2; N, 11.5. $C_{12}H_{10}N_2O_4$ requires C, 58.5; H, 4.2; N, 11.4%).

3d: orange tiny needles, mp 81 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2250 (CN), 1725 (CO); δ_H 1.38 (3 H, d, $J = 6.2$, CH_3), 1.40 (3 H, d, $J = 6.2$, CH_3), 5.26 (1 H, t, $J = 6.2$ Hz, OCH), 7.61–7.94 (3 H, m, ArH), 8.24–8.36 (1 H, m, ArH), 8.72 (1 H, s, —CH═) (Found: C, 60.2; H, 4.5; N, 10.7. $C_{13}H_{12}N_2O_4$ requires C, 60.0; H, 4.7; N, 10.8%).

3e: orange prisms, mp 44–46 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2230 (CN), 1730 (CO); δ_H 0.99 (3 H, t, $J = 6.2$, CH_3), 1.43–1.78 (4 H, m, CH_2CH_2), 4.37 (2 H, $J = 6.4$ Hz, OCH_2), 7.72–7.89 (3 H, m, ArH), 8.23–8.26 (1 H, m, ArH), 8.73 (1 H, s, —CH═) (Found: C, 61.5; H, 5.0; N, 10.4. $C_{14}H_{14}N_2O_4$ requires C, 61.3; H, 5.1; N, 10.2%).

3f: light tan tiny needles, mp 111–113 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2240 (CN), δ_H 6.30 (2 H, s, OCH_2O), 7.21 (1 H, s, ArH), 7.77 (1 H, s, ArH), 8.35 (1 H, s, —CH═) (Found: C, 54.1; H, 2.1; N, 17.4. $C_{11}H_5N_3O_4$ requires C, 54.3; H, 2.1; N, 17.3%).

3g: yellow needles, mp 162–164 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2230 (CN), 1740 (CO); δ_H 3.97 (3 H, s, OCH_3), 6.26 (2 H, s, OCH_2O), 7.27 (1 H, s, ArH), 7.72 (1 H, s, ArH), 8.85 (1 H, s, —CH═) (Found: C, 52.3; H, 2.8; N, 10.4. $C_{12}H_8N_2O_6$ requires C, 52.2; H, 2.9; N, 10.1%).

3h: yellow tiny needles, mp 139–140 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2240 (CN), 1730 (CO); δ_H 1.42 (3 H, t, $J = 7.1$, CH_3), 4.42 (2 H, q, $J = 7.1$ Hz, OCH_2), 6.26 (2 H, s, OCH_2O), 7.25 (1 H, s, ArH), 7.72 (1 H, s, ArH), 8.64 (1 H, s, —CH═) (Found: C, 53.7; H, 3.6; N, 9.6. $C_{13}H_{10}N_2O_6$ requires C, 53.8; H, 3.5; N, 9.7%).

3i: light tan needles, mp 112–113 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2250 (CN), 1725 (CO); δ_H 1.40 (6 H, d, $J = 6.4$, $2 \times CH_3$), 5.22 (1 H, $J = 6.4$ Hz, OCH), 6.25 (2 H, s, OCH_2O), 7.25 (1 H, s, ArH), 7.70 (1 H, s, ArH), 8.60 (1 H, s, —CH═) (Found: C, 55.3; H, 4.1; N, 9.1. $C_{14}H_{12}N_2O_6$ requires C, 55.3; H, 4.0; N, 9.2%).

3j: light tan tiny needles, mp 98–99 °C; $\tilde{\nu}_{max}/cm^{-1}$ 2250 (CN), 1725 (CO); δ_H 0.99 (3 H, t, $J = 6.4$, CH_3), 1.31–1.81 (4 H, m, CH_2CH_2), 4.35 (2 H, t, $J = 6.4$ Hz, OCH_2), 6.25 (2 H, s, OCH_2O), 7.30 (1 H, s, ArH), 7.71 (1 H, s, ArH), 8.62 (1 H, s, —CH═) (Found: C, 56.8; H, 4.3; N, 8.7. $C_{15}H_{14}N_2O_6$ requires C, 56.6; H, 4.4; N, 8.8%).

General Procedure for Synthesis of 2-*Aminoquinoline*-3-*carboxylic Acid Derivatives* **4**.—$TiCl_4$ (1.65 ml, 15 mmol) was added dropwise using a syringe to a stirred suspension of zinc power (1.95 g, 30 mmol) in freshly distilled dry THF (20 ml) at RT under a N_2 atmosphere. The mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to RT and a solution of nitrocyano olefin **3** (5 mmol) in THF (3 ml) was added carefully. On completion of the reaction most of the solvent was removed in vacuum. The residue was poured into 10% K_2CO_3 (100 ml) and extracted with $CHCl_3$ (4×30 ml). The combined organic layer was washed with water (2×20 ml), dried (Na_2SO_4), and the solvent removed to give the crude product, which was purified by recrystallization from an appropriate solvent.

4a: Light tan prisms, mp 226–227 °C (from ethyl acetate and acetone); $\tilde{\nu}_{max}/cm^{-1}$ 3400 (NH_2), 3160 (NH_2), 2230 (CN); δ_H 5.46 (2 H, br s, NH_2), 7.32–7.71 (4 H, m, ArH), 8.30 (1 H, s, hetero ArH); *m*/*z* 170 ($M + 1$, 22), 169 (M^+, 100), 144 (73), 143 (34), 117 (20), 116 (33%) (Found: C, 70.9; H, 4.4; N, 24.8. $C_{10}H_7N_3$ requires C, 71.0; H, 4.2, N, 24.8%).

4b: yellow crystals, mp 139–140 °C (from EtOH, lit.[13] 140–141 °C); $\tilde{\nu}_{max}/cm^{-1}$ 3380 (NH_2), 3200 (NH_2), 1700 (CO); δ_H 3.93 (3 H, s, OCH_3), 6.80 (2 H, br s, NH_2), 7.03–7.68 (4 H, m, ArH), 8.66 (1 H, s, hetero ArH).

4c: yellow needles, mp 134–135 °C (from EtOH lit.[13] 135 °C); $\tilde{\nu}_{max}/cm^{-1}$ 3450 (NH_2), 3180 (NH_2), 1700 (CO); δ_H 1.41 (3 H, t, $J = 7.2$, CH_3), 4.40 (2 H, q, $J = 7.2$ Hz, OCH_2), 6.68 (2 H, br s, NH_2), 7.10–7.82 (4 H, m, ArH), 8.69 (1 H, s, hetero ArH); *m*/*z* 217 ($M + 1$, 14), 216 (M^+, 100), 171 (18), 170 (32), 144 (75), 143 (65), 116 (36). 89 (23%).

4d: orange prisms, mp 160–161 °C (from EtOH); $\tilde{\nu}_{max}/cm^{-1}$ 3415 (NH_2), 3150 (NH_2), 1690 (CO); δ_H 1.41 (6 H, d, $J = 6.2$, $2 \times CH_2$), 5.28 (1 H, $J = 6.2$ Hz, OCH), 6.66 (2 H, br s, NH_2), 7.24–7.70 (4 H, m, ArH), 8.65 (1 H, s, hetero ArH); *m*/*z* 231 ($M + 1$, 15), 230 (M^+, 81), 188 (5), 171 (14), 144 (100), 143 (51), 117 (21), 116 (32%) (Found: C, 67.6; H, 6.2; N, 12.3. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%).

4e: yellow crystals, mp 104–106 °C (from EtOH); $\tilde{\nu}_{max}/cm^{-1}$ 3380 (NH_2), 3150 (NH_2), 1690 (CO); δ_H 1.00 (3 H, t, $J = 6.9$, CH_3), 1.44–1.68 (4 H, m, CH_2CH_2), 4.35 (2 H, t, $J = 6.4$ Hz, OCH_2), 6.79 (2 H, br s, NH_2), 7.20–7.71 (4 H, m, ArH), 8.66 (1 H, s, hetero ArH); *m*/*z* 245 ($M + 1$, 11), 244 (M^+, 68), 188 (6), 171 (15), 144 (100), 143 (52), 117 (23), 116 (35%) (Found: C, 69.0; H, 6.7; N, 11.4. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%).

4f: tan crystals, mp 280 °C (decomp.) (from ethyl acetate and EtOH); $\tilde{\nu}_{max}/cm^{-1}$ 3400 (NH_2), 3160 (NH_2), 2230 (CN); δ_H 6.14 (2 H, s, OCH_2O), 6.66 (2 H, br s, NH_2), 6.91 (1 H, s, ArH), 7.12 (1 H, s, ArH), 8.37 (1 H, s, hetero ArH) (Found: C, 62.2; H, 3.2; N, 19.5. $C_{11}H_7N_3O_2$ requires C, 62.0; H, 3.3; N, 19.7%).

4g: yellow crystals, mp 225–227 °C (from EtOH); $\tilde{\nu}_{max}/cm^{-1}$ 3400 (NH_2), 3150 (NH_2), 1680 (CO); δ_H 3.93 (3 H, s, OCH_3), 6.05 (2 H, s, OCH_2), 6.67 (2 H, br, s, NH_2), 6.92 (1 H, s, ArH), 6.99 (1 H, s, ArH), 8.49 (1 H, s, hetero ArH); *m*/*z* 247 ($M + 1$, 21), 246 (M^+, 44), 215 (27), 214 (45), 188 (44), 187 (100), 161 (12), 160 (30%) (Found: C, 58.4; H, 4.2; N, 11.5. $C_{12}H_{10}N_2O_4$ requires C, 58.5; H, 4.1; N, 11.4%).

4h: yellow crystals, mp 204–205 °C (from ethyl acetate); $\tilde{\nu}_{max}/cm^{-1}$ 3440 (NH_2), 3280 (NH_2), 1680 (CO); δ_H 1.41 (3 H, t, $J = 7.1$, CH_3), 4.38 (2 H, q, $J = 7.1$ Hz, OCH_2), 6.03 (2 H, s, OCH_2O), 6.56 (2 H, br s, NH_2), 6.90 (1 H, s, ArH), 6.95 (1 H, s, ArH), 8.46 (1 H, s, hetero ArH); *m*/*z* 261 ($M + 1$, 20), 276 (M^+, 100), 232 (6), 215 (9), 214 (11), 188 (72), 161 (7), 160 (20%) (Found: C, 60.3; H, 4.5; N, 10.7. $C_{13}H_{12}N_2O_4$ requires C, 60.0; H, 4.6; N, 10.8%).

4i: yellow crystals, mp 215–217 °C (from EtOH); $\tilde{\nu}_{max}/cm^{-1}$ 3380 (NH_2), 3200 (NH_2), 1680 (CO); δ_H 1.38 (6 H, d, $J = 6.2$, $2 \times CH_3$), 5.26 (1 H, $J = 6.2$ Hz, OCH), 6.03 (2 H, s, OCH_2O), 6.54 (2 H, br s, NH_2), 6.91 (1 H, s, ArH), 6.95 (1 H, s, ArH), 8.44 (1 H, s, hetero ArH); *m*/*z* 275 ($M + 1$, 6), 274 (M^+, 94), 232 (9), 215 (11), 214 (9), 188 (100), 187 (38), 161 (6), 160 (25%) (Found: C, 61.4; H, 5.1; N, 10.3. $C_{14}H_{14}N_2O_4$ requires C, 61.3; H, 5.1; N, 10.2%).

4j: yellow crystals, mp 148–149 °C (from EtOH); $\tilde{\nu}_{max}/cm^{-1}$ 3480 (NH_2), 3200 (NH_2), 1680 (CO); δ_H 1.00 (3 H, t, $J = 6.8$, CH_3), 1.21–1.78 (4 H, m, CH_2CH_2), 4.32 (2 H, t, $J = 6.4$ Hz, OCH_2), 6.02 (2 H, s, OCH_2O), 6.55 (2 H, br s, NH_2), 6.89 (1 H, s, ArH), 6.93 (1 H, s, ArH), 8.42 (1 H, s, hetero ArH); *m*/*z* 289 ($M + 1$, 17), 288 (M^+, 90), 232 (11), 216 (7), 215 (11), 188 (100), 187 (31), 161 (8), 160 (23) (Found: C, 62.4; H, 5.7; N, 9.6. $C_{15}H_{16}N_2O_4$ requires C, 62.5; H, 5.6; N, 9.7%).

We are grateful to the Education Committee Nature Science Foundation of Jiangsu province for financial support.

Received, 21st January 1998; Accepted, 12th April 1998
Paper E/8/00588E

References

1 J. E. McMurry, *Chem. Rev.*, 1989, **89**, 1513; D. Lenoir, *Synthesis*, 1989, **883**.

2 L. H. Zhou, D. Q. Shi, Y. Gao, W. B. Shen, G. Y. Dai and W. X. Chen, *Tetrahedron Lett.*, 1997, **38**, 2729.

3 L. H. Zhou, S. J. Tu, D. Q. Shi, G. Y. Dai and W. X. Chen, *Synthesis*, in press.

4 I. Arai and I. Nakayama, *J. Pharm. Soc. Jpn.*, 1952, **72**, 167; N. Yoshida and S. Ishii, *J. Biochem.*, 1972, **71**, 185; T. Matsumoto, D. Yoshida, S. Mitzusaki and H. Tomita, *Agric. Biol. Chem.*, 1978, **42**, 861.

5 J. R. Pfister, *J. Nat. Prod.*, 1988, **51**, 969.

6 D. G. Markees, V. C. Dewey and G. W. Kidder, *J. Med. Chem.*, 1970, **13**, 324.

7 A. A. Alhaider, M. A. Abdelkader and E. J. Lien, *J. Med. Chem.*, 1985, **28**, 1398; K. Hino, Y. Nagai and H. Uno, *Chem. Pharm. Bull.*, 1987, **35**, 2819.

8 S. F. Campbell, J. D. Hardstone and M. J. Palmer, *J. Med. Chem.*, 1988, **31**, 1031.

9 (*a*) S. Gorbadjiev, Ch. Ivanov and B. Moskova, *Synth. Commun.*, 1985, **15**, 451; (*b*) S. Gorbadjiev, Ch. Ivanov and B. Moskova, *Synth. Commun.*, 1987, **17**, 1363; (*c*) A. A. Sayed, *Synth. Commun.*, 1991, **21**, 749; (*d*) F. Korodi, *Synth. Commun.*, 1991, **21**, 1841.

10 W. X. Chen, J. H. Zhang, M. Y. Hu and X. C. Wang, *Synthesis*, 1990, 701; J. X. Chen, J. P. Jiang, W. X. Chen and T. Y. Gao, *Heterocycles*, 1991, **32**, 2339.

11 J. George and S. Chandrascharan, *Synth. Commun.*, 1983, **13**, 495.

12 G. Y. Dai, D. Q. Shi and L. H. Zhou, *Chin. J. Appl. Chem.*, 1995, **12**, 103.

13 J. M. Tyler, *J. Chem. Soc.*, 1955, 203.