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Facile Synthesis of Substituted Quinazolin-4-(3H)-ones Using Low-Valence Titanium Reagent

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ABSTRACT

A short and facile synthesis of a series of 3-aryl quinazolin-4-(3H)-ones was accomplished in good yields via the intermolecular reductive coupling reaction of N-aryl-2-nitrobenzamide and triethyl orthoformate promoted by $TiCl_4/Zn$.

Key Words: Quinazolin-4-(3H)-ones; Low-valence titanium; Synthesis.

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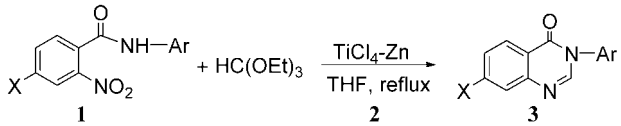
INTRODUCTION

In the early seventies, three groups of investigators[1–3] established that low-valence titanium, prepared by the reaction of strong reducing agents on titanium trichloride or titanium tetrachloride in tetrahydrofuran, can abstract oxygen from ketones or aldehydes, leading to formation of olefins. An increasing interest in the reaction induced by low-valence titanium reagents is observed and a large number of functional groups can be reduced.[4–8] Recently, we reported the cyclodimerization of α,β-unsaturated ketones and α,β-unsaturated nitrile compounds promoted by this reagent, yield functional cyclopentanes[9] and cyclopentenes,[10] respectively.

Quinazolin-4-(3H)-one is an alkaloid.[11,12] Substituted quinazolin-4-(3H)-ones possess a wide range of pharmacological activities. 2-Methyl-3-*o*-toly-quinazolin-4-(3H)-one is a potent hypnotic agent and other quinazolin-4-(3H)-ones have been reported to exhibit analgesic, antibacterial, anticancer, anesthetic, anticonvulsant, anti-inflammatory, antimalarial, and antiparasitic, diuretic, sedative and tranquilizing properties [for selected examples, see Refs.[13–20]]. The main synthetic approaches to such compounds consist of preliminary amidation of 2-amninobenzonitrile, 2-aminobenzoic acid, or ethyl 2-aminobenzoate[21–23] and thermolysis of 4-amilino-1,2,3-benzotriazimes.[24] Different one-pot synthesis have been described, but the condensation of 2-aminobenzoic acid with amides or nitriles requires either high temperature or must be affected in a sealed tube at 200°C.[25–27] Unfortunately, synthetic methods for the elaboration of this bicyclic system are not general in scope, and involve often low-yielding multistep and reaction sequences. We wish to report here a facile synthesis of 3-arylquinazolin-4-(3H)-ones in fairly high yields via the reaction of N-aryl-2-nitrobenzamide and triethyl orthoformate promoted by low-valence titanium.

When N-aryl-2-nitrobenzamide (**1**) and triethyl orthoformate (**2**) were treated with low-valence titanium, prepared from titanium tetrachloride and zinc powder in anhydrous THF, the intermolecular reductive coupling product (**3**) are obtained in moderate yields (Sch. 1). The results are summarized in Table 1.



1 **2** **3**

Scheme 1.

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Table 1. The synthesis of 3-arylquinazolin-4-(3H)-ones promoted by low-valence titanium.

Entry	X	Ar	Yield (%)[a]
3a	H	C_6H_5	84
3b	H	4-$CH_3C_6H_4$	84
3c	H	4-ClC_6H_4	86
3d	H	3-Cl-4-F-C_6H_3	79
3e	Cl	C_6H_5	90
3f	Cl	4-$CH_3C_6H_4$	93
3g	Cl	4-ClC_6H_4	91
3h	Cl	4-BrC_6H_4	87
3i	Cl	3-Cl-4-F-C_6H_3	83

[a]Isolated yield.

All the products **3a–i** were characterized by IR, ^{1}H NMR spectral analysis, and elemental analysis. The structure of **3a** was confirmed by x-ray analysis.[a] The x-ray crystal structure of **3a** is given in Fig. 1.

In conclusion, we believe that the above work provides a useful method for preparing 3-arylquinazolin-4-(3H)-ones. The remarkable advantage of this reaction is neutral and mild reaction conditions and simple operation. Further studies to develop other new uses of the low-valence titanium reagent are now in progress.

EXPERIMENTAL

THF was distilled from sodium benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. ^{1}H NMR spectra were recorded on an Inova-400 instrument as $CDCl_3$ solutions using TMS as internal standard. IR spectra were determined on Tensor 27 spectrometer. Elemental analyses were performed on Perkin–Elmer 2400 II instrument. X-ray diffraction was measure on a Siemens P4 diffractometer.

[a]X-ray crystallography for **3a**: Empirical formula $C_{14}H_{10}N_2O$, $F_W = 222.24$, $T = 297(2)$ K, moloclinic, space group $P2(1)/c$, $a = 12.080(2)$ Å, $b = 7.793(1)$ Å, $c = 11.599(1)$ Å, $\beta = 97.56(1)^\circ$, $V = 1082.4(2)$ Å^3, $Z = 4$, $D_c = 1.364\,mg/m^3$, λ(Mo Kα) = 0.71073 Å, $\mu = 0.088\,mm^{-1}$, $F(0\ 0\ 0) = 464$. $170^\circ < \theta < 25.25^\circ$, $R = 0.0358$, $wR = 0.0851$, $S = 0933$. Largest diff. Peak and hole: 0.130 and $-0.117e$ Å^{-3}.

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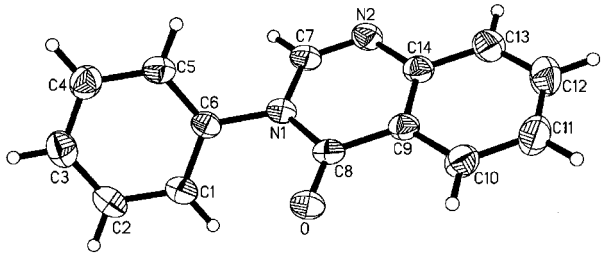

Figure 1. The x-ray crystal structure of **3a**.

General Procedure for the Synthesis of 3-Arylquinazolin-4(3H)-ones (3)

$TiCl_4$ (2.2 mL, 20 mmol) was added dropwise using a syringe to a stirred suspension of zinc dust (2.6 g, 40 mmol) in freshly distilled anhydrous THF (15 mL) at room temperature under a dry nitrogen atmosphere. After completion of the addition, the mixture was refluxed for 2 hr. The suspension of the low-valence titanium reagent formed was cooled to room temperature and a solution of N-aryl-2-nitrobenzamide (5 mmol) and triethyl orthoformate (10 mmol) in THF (10 mL) was added dropwise. The mixture was refluxed 5 hr under N_2 (the reaction was monitored by TLC). The reaction mixture was quenched with 10% HCl (50 mL) and extracted with $CHCl_3$ (3×50 mL). The combined extracts were washed, with water (3×50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products **3a–i** were purified by recrystallization from 95% ethanol.

3a. M.p. 135–137°C (lit.[28] m.p. 138–139°C); IR (KBr, ν, cm^{-1}): 3030, 1672, 1610, 1473, 1402, 1262, 1181, 1111, 1024, 933, 913, 767, 699, 623; ^1H NMR ($CDCl_3$, δ, ppm): 7.43–7.46 (2H, m, Ar-H), 7.51–7.59 (4H, m, Ar-H), 7.77–7.85 (2H, m, Ar-H), 8.15 (1H, s, C_2-H), 8.38 (1H, d, $J = 11$ Hz, C_5-H).

3b. M.p. 147–149°C (lit.[28] m.p. 148–149°C); IR (KBr, ν, cm^{-1}): 3030, 1689, 1600, 1514, 1471, 1323, 1293, 1192, 1114, 1025, 917, 836, 817, 770, 749, 694, 615; ^1H NMR ($CDCl_3$, δ, ppm): 2.44 (3H, s, CH_3), 7.26–7.37 (4H, m, Ar-H), 7.54–7.58 (1H, m, Ar-H), 7.76–7.81 (2H, m, Ar-H), 8.13 (1H, s, C_2-H), 8.38 (1H, d, $J = 6.8$ Hz, C_5-H).

3c. M.p. 183–183°C (lit.[29] m.p. 180–181°C); IR (KBr, ν, cm^{-1}): 3030, 1695, 1614, 1490, 1467, 1293, 1257, 1178, 1093, 1012, 918, 828, 765, 695; ^1H NMR ($CDCl_3$, δ, ppm): 7.38–7.40 (2H, m, Ar-H), 7.53–7.59 (3H, m, Ar-H), 7.77–7.85 (2H, m, Ar-H), 8.10 (1H, s, C_2-H), 8.37 (1H, d, $J = 8.8$ Hz, C_5-H).

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3d. M.p. 212–214°C; IR (KBr, ν, cm^{-1}): 3030, 1699, 1612, 1500, 1474, 1324, 1259, 871, 822, 771, 752, 717, 692; ^1H NMR ($CDCl_3$, δ, ppm): 7.33–7.35 (2H, m, Ar-H), 7.54–7.61 (2H, m, Ar-H), 7.79–7.86 (2H, m, Ar-H), 8.11 (1H, s, C_2-H), 8.37 (1H, d, $J = 7.2$ Hz, C_5-H), Elemental analysis: found (%): C, 61.38; H, 2.73, Calcd for $C_{24}H_8ClFN_2O$ (274.68): C, 61.22; H, 2.94.

3e. M.p. 196–198°C; IR (KBr, ν, cm^{-1}): 3030, 1677, 1606, 1454, 1387, 1255, 1078, 899, 863, 781, 749, 698; ^1H NMR ($CDCl_3$, δ, ppm): 7.42–7.43 (2H, m, Ar-H), 7.51–7.59 (4H, m, Ar-H), 7.78 (1H, s, C_8-H), 8.16 (1H, s, C_2-H), 8.35 (1H, d, $J = 8.4$ Hz, C_5-H), Elemental analysis: found (%): C, 65.58; H, 3.34, Calcd for $C_{14}H_9ClN_2O$ (256.69): C, 65.51; H, 3.53.

3f. M.p. 191–192°C; IR (KBr, ν, cm^{-1}): 3030, 1677, 1597, 1513, 1464, 1387, 1257, 1132, 1078, 1057, 951, 920, 899, 864, 831, 781, 765, 691; ^1H NMR ($CDCl_3$, δ, ppm): 2.45 (3H, s, CH_3), 7.26–7.30 (2H, m, Ar-H), 7.35–7.37 (2H, m, Ar-H), 7.50 (1H, d, $J = 8.4$ Hz, C_6-H), 7.77 (1H, s, C_8-H), 8.13 (1H, s, C_2-H), 8.30 (1H, d, $J = 8.4$ Hz, C_5-H), Elemental analysis: found (%): C, 66.73; H, 4.01, Calcd for $C_{15}H_{11}ClN_2O$ (270.71): C, 66.55; H, 4.09.

3g. M.p. 211–213°C; IR (KBr, ν, cm^{-1}): 3033, 1692, 1610, 1489, 1408, 1302, 1257, 1175, 1082, 896, 834, 814, 789, 776; ^1H NMR ($CDCl_3$, δ, ppm): 7.38 (2H, d, $J = 8.0$ Hz, Ar-H), 7.52–7.55 (3H, m, Ar-H), 7.79 (1H, s, C_8-H), 8.12 (1H, s, C_2-H), 8.29 (1H, d, $J = 8$ Hz, C_5-H), Elemental analysis: found (%): C, 57.91; H, 2.53, Calcd for $C_{14}H_8Cl_2N_2O$: C, 57.76; H, 2.77.

3h. M.p. 237–238°C; IR (KBr, ν, cm^{-1}): 3030, 1690, 1607, 1485, 1258, 1069, 1009, 897, 855, 814, 768, 694, 625; ^1H NMR ($CDCl_3$, δ, ppm): 7.31 (2H, d, $J = 8.4$ Hz, Ar-H), 7.52 (1H, d, $J = 8.8$ Hz, C_6-H), 7.69 (2H, d, $J = 8.4$ Hz, Ar-H), 7.78 (1H, s, C_8-H), 8.11 (1H, s, C_2-H), 8.29 (1H, d, $J = 8.8$ Hz, C_5-H), Elemental analysis: found (%): C, 50.35; H, 2.16, Calcd for $C_{14}H_8BrClN_2O$ (335.58): C, 50.11; H, 2.40.

3i. M.p. 198–200°C; IR (KBr, ν, cm^{-1}): 3030, 1697, 1610, 1503, 1257, 824, 780; ^1H NMR ($CDCl_3$, δ, ppm): 7.32–7.35 (2H, m, Ar-H), 7.53–7.55 (2H, m, Ar-H), 7.80 (1H, s, C_8-H), 8.12 (1H, s, C_2-H), 8.29 (1H, d, $J = 8.8$ Hz, C_5-H), Elemental analysis: found (%): C, 54.58; H, 2.13, Calcd for $C_{14}H_7Cl_2FN_2O$ (309.12): C, 54.40; H, 2.28.

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