SHORT PAPER

J. Chem. Research (S), 2003, 366–367

A novel reductive cross-coupling reaction of *N*-aryl-2-nitrobenzamide and triethyl orthoformate promoted by the $TiCl_4$/Sm system: an access to 3-arylquinazolin-4 (3H)-ones

Daqing Shi[a,b,c]*, Liangce Rong[b,c], Juxian Wang[b,c], Qiya Zhuang[b,c] and Hongwen Hu[a]

[a]*Department of Chemistry , Nanjing University, Nanjing, 210093, P. R. China*

[b]*Department of Chemistry , Xuzhou Normal University, Xuzhou , 221009, P. R. China*

[c]*Key Laboratory of Biotechnology on Medical Plant, Jiangsu Xuzhou , 221009, P. R. China*

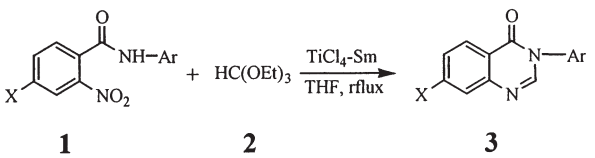
A short and facile synthesis of a series of 3-arylquinazolin-4(3H)-ones was accomplished in good yield via the intermolecular reductive coupling reaction of N-aryl-2-nitrobenzamide and triethyl orthoformate promoted by $TiCl_4$/Sm.

Keywords: quinazolin-4(3H)-ones, low-valent titanium, 2-nitrobenzamide

In recent years an increasing interest in the reactions induced by low-valent titanium reagents has occurred because of its exceedingly high efficacy in the reductive coupling of carbonyl compounds[1]. A variety of other functional groups can also be reacted[2-5]. Recently, we have reported the low-valent titanium-induced intermolecular reductive coupling reaction of carboxylic derivatives with aromatic ketones[6], the intramolecular reductive coupling reaction of 4,4-dicyano-1,3- diaryl-1-butanone[7] and the cyclodimerization of α,β-unsaturated ketones[8].

Quinazolin-4(3*H*)-ones are in demand because of their potential biological and pharmaceutical activities.[9-11] Unfortunately, synthetic methods for the elaboration of this bicyclic system of rather simple structure are not general in scope, and involve multistep, and often low-yielding, reaction sequences. The main synthetic approaches to such compounds consist of preliminary amidation of 2-aminobenzonitrile, 2-aminobenzoic acid or ethyl 2-aminobenzoate[12-14] and the aza-Wittig reactions of α-azido- substituted aromatic imides.[15-16] Different one-pot syntheses have been described, but the condensation of 2-aminobenzoic acid with amides, thioamides or nitriles requires either high temperature or must be effected in a sealed tube at 200˚C.[17-19] Recently, some reactions induced by the $TiCl_4$/Sm system have been reported in the literature.[20-21] Here we wish to describe a new method induced by the $TiCl_4$/Sm system for the preparation of 3-arylquinazolin-4(3*H*)-ones using *N*-aryl-2-nitro- benzamides as the starting material.

When *N*-aryl-2-nitrobenzamides **1** and triethyl orthoformate **2** were treated with low-valent titanium, prepared from titanium tetrachloride and samarium powder in anhydrous THF, the reductive cyclisation product 3-aryl- quinazolin-4(3*H*)-ones **3** were obtained in good yield (Scheme 1). The results are summarized in Table 1.



1 **2** **3**

Scheme 1

Table 1 The synthesis of 3-arylquinazolin- 4(3*H*)-ones promoted by $TiCl_4$/Sm

Entry	X	Ar	Isolated yield/%
3a	H	C_6H_5	82
3b	H	4-$CH_3C_6H_4$	86
3c	H	4-ClC_6H_4	84
3d	H	3-Cl-4-F-C_6H_3	81
3e	Cl	C_6H_5	92
3f	Cl	4-$CH_3C_6H_4$	93
3g	Cl	4-ClC_6H_4	90
3h	Cl	4-BrC_6H_4	89
3i	Cl	3-Cl-4-F-C_6H_3	85

In conclusion, we believe that the above work provides a useful method for preparing 3-arylquinazolin-4(3*H*)-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

Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All reactions were performed under a nitrogen atmosphere. Melting points were uncorrected. ^{1}H NMR spectra were determined on a Inova-400 spectrometer as $CDCl_3$ solutions. *J* Values are in hertz. Chemical shifts are expressed in ppm downfield from internal TMS. Microanalyses were carried out using a Perkin-Elmer 2400 II analyzer. IR spectra were recorded on an FTIR-8101 spectrometer in KBr with absorptions in cm^{-1}.

General procedure for the synthesis of 3-arylquinazolin-4(3H)-ones (3): $TiCl_4$ (1.1ml, 10mmol) was added dropwise using a syringe to a stirred suspension of Samariam dust (1.5g, 10mmol) in freshly distilled anhydrous THF (15ml) at room temperature under a dry nitrogen atmosphere. After completion of the addition, the mixture was refluxed for 2h. The suspension of the low-valence titanium reagent formed was cooled to room temperature and a solution of *N*-aryl-2-nitrobenzamide (3mmol) and triethyl orthoformate (6mmol) in THF (10ml) was added dropwise. The mixture was refluxed for 5h under N_2 (the reaction was monitored by TLC). The reaction mixture was quenched with 10% HCl (50ml) and extracted with $CHCl_3$ (3×50ml). The combined extracts were washed with water (3×50ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products **3a–i** were purified by recrystallisation from 95% ethanol.

3-phenylquinazolin-4(3H)-one (**3a**): m.p. 140–142°C(lit.[22] m.p. 138–139°C). IR, ν: 3030, 1672, 1610, 1473, 1402, 1262, 1181, 1111, 1024, 933, 913, 767, 699, 623. ^{1}H NMR: 7.43∼7.46(2H, m, H-2'/H-6'), 7.51∼7.54(3H, m, H-3'/H-5'), 7.57(1H, dd, J_1=8.4Hz,

* To receive any correspondence. E-mail: dqshi@xznu.edu.cn

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

J_2=7.6Hz, H-6), 7.78(1H, d, *J*=8.4Hz, H-8), 7.81(1H, dd, J_1=7.6Hz, J_2=8.4Hz, H-7), 8.15(1H, s, H-2), 8.38(1H, d, *J*=8.4Hz, H-5).

3-(4'-methylphenyl)quinazolin-4(3H)-one (**3b**): m.p.147–149°C (lit.[22] m.p. 148–149°C). IR, ν: 3030, 1689, 1600, 1514, 1471, 1323, 1293, 1192, 1114, 1025, 917, 836, 817, 770, 749, 694, 615. ^{1}H NMR: 2.44(3H, s, CH_3), 7.31(2H, d, *J*=8.4Hz, H-2'/H-6'), 7.36(2H, d, *J*=8.4Hz, H-3'/H-5'), 7.55(1H, dd, J_1=8.4Hz, J_2=8.4Hz, H-6), 7.77(1H, d, *J*=8.4Hz H-8), 7.81(1H, dd, J_1=8.4Hz, J_2=8.4Hz, H-7), 8.13(1H, s, H-2), 8.38(1H, d, *J*=8.4 Hz, H-5).

3-(4'-chlorophenyl)quinazolin-4(3H)-one (**3c**): m.p. 182–183°C (lit.[23] m.p. 180–181°C). IR, ν: 3030, 1695, 1614, 1490, 1467, 1293, 1257, 1178, 1093, 1012, 918, 828, 765, 695. ^{1}H NMR:7.39(2H, d, *J*=8.4Hz, H-2'/H-5'), 7.54(2H, d, *J*=8.4Hz, H-3'/H-5'), 7.57(1H, dd, J_1=8.4Hz, J_2=8.8Hz, H-6), 7.78(1H, d, *J*=7.2Hz, H-8), 7.82(1H, dd, J_1=7.2Hz, J_2=8.4Hz, H-7), 8.10(1H, s, H-2), 8.37(1H, d, *J*=8.8 Hz, H-5).

3-(3'-chloro-4'-fluorophenyl)quinazolin-4(3H)-one (**3d**): m.p. 212–214°C. IR, ν: 3030, 1699, 1612, 1500, 1474, 1324, 1259, 871, 822, 771, 752, 717, 692. ^{1}H NMR: 7.32(1H, s, H-2'), 7.34(1H, d, *J*=7.2Hz, H-6'), 7.55(1H, d, *J*=7.2Hz, H-5'), 7.59(1H, dd, J_1=8.4Hz, J_2=7.6Hz, H-6), 7.80(1H, d, *J*=7.6Hz, H-8), 7.84(1H, dd, J_1=7.6Hz, J_2=7.6Hz, H-7), 8.11(1H, s, H-2), 8.37(1H, d, *J*=8.4 Hz, H-5). Anal. Calc. for $C_{14}H_8ClFN_2O$: C, 61.22; H, 2.94; N, 10.20; Found: C, 61.38; H, 2.73; N, 10.38%.

7-chloro-3-*phenylquinazolin-4(3H)-one* (**3e**): m.p. 196–197°C. IR, ν: 3030, 1677, 1606, 1454, 1387, 1255, 1078, 899, 863, 781, 749, 698. ^{1}H NMR: 7.42(2H, d, *J*=7.2Hz, H-2'/H-6'),7.52 (1H, d, *J*=8.4Hz, H-6), 7.57(3H, t, *J*=7.2Hz, H-3'/H-4'/H-5'), 7.78(1H, s, H-8), 8.16(1H, s, H-2), 8.35(1H, d, *J*=8.4 Hz, H-5). Anal. Calc. for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91; Found: C, 65.58; H, 3.34; N, 11.03%.

7-chloro-3-*(4'-methylphenyl)quinazolin-4(3H)-one* (**3f**): m.p. 194–195°C. IR, ν: 3030, 1677, 1597, 1513, 1464, 1387, 1257, 1132, 1078, 1057, 951, 920, 899, 864, 831, 781, 765, 691. ^{1}H NMR: 2.45(3H, s, CH_3), 7.29(2H, d, *J*=7.6Hz, H-2'/H-6'), 7.36(2H, d, *J*=7.6Hz, H-3'/H-5'), 7.50(1H, d, *J*=8.4 Hz, H-6), 7.77(1H, s, H-8), 8.13(1H, s, H-2), 8.30(1H, d, *J*=8.4 Hz, H-5). Anal. Calc. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.09; N, 10.35; Found: C, 66.73; H, 4.01; N, 10.47%.

7-chloro-3-*(4'-chlorophenyl)quinazolin-4(3H)-one* (**3g**): m.p. 213–214°C. IR, ν: 3033, 1692, 1610, 1489, 1408, 1302, 1257, 1175, 1082, 896, 834, 814, 789, 776. ^{1}H NMR: 7.38(2H, d, *J*=8.0 Hz, H-2'/H-6'), 7.52((1H, d, *J*=8.0 Hz, H-6), 7.54(2H, d, *J*=8.0 Hz, H-3'/H-5') 7.79(1H, s, H-8), 8.12(1H, s, H-2), 8.29(1H, d, *J*=8.0Hz, H-5). Anal. Calc. for $C_{14}H_8Cl_2N_2O$: C, 57.76; H, 2.77; N, 9.62; Found: C, 57.91; H, 2.53; N, 9.58%.

7-chloro-3-*(4'-bromophenyl)quinazolin-4(3H)-one* (**3h**): m.p. 235–237°C. IR, ν: 3030, 1690, 1607, 1485, 1258, 1069, 1009, 897, 855, 814, 768, 694, 625. ^{1}H NMR: 7.31(2H, d, *J*=8.4 Hz, H-2'/H-6'), 7.52(1H, d, *J*=8.8 Hz, H-6), 7.69(2H, d, *J*=8.4 Hz, H-3'/H-5'), 7.78(1H, s, H-8), 8.11(1H, s, H-2), 8.29(1H, d, *J*=8.8 Hz, H-5). Anal. Calc. for $C_{14}H_8BrClN_2O$: C, 50.11; H, 2.40; N, 8.35; Found: C, 50.35; H, 2.16; N, 8.43%.

7-chloro-3-*(3'-chloro-4'-fluorophenyl)quinazolin-4(3H)-one* (**3i**): m.p. 197–198°C. IR, ν: 3030, 1697, 1610, 1503, 1257, 824, 780. ^{1}H NMR: 7.33(1H, s, H-2'), 7.34(1H, d, *J*=8.8 Hz, H-6'), 7.54(2H, d, *J*=8.8 Hz, H-5'/H-6), 7.80(1H, s, H-8), 8.12(1H, s, H-2), 8.29(1H, d, *J*=8.8 Hz, H-5). Anal. Calc. for $C_{14}H_7Cl_2FN_2O$: C, 54.40; H, 2.28; N, 9.06; Found: C, 54.58; H, 2.13; N, 8.92%.

We thank the "Surpassing Project" of Jiangsu Province, the Natural Science Foundation of the Education Committee of Jiangsu Province (00KJB150008) and the Key Laboratory of Organic Synthesis, Suzhou University for financial support.

Received 30 November 2002; accepted 26 February 2003
Paper 02/1682

References

1 J.E. McMuny, *Chem. Rev.*, 1989, **89**, 1513.
2 D. Lenour, *Synthesis*, 1989, 883.
3 D.Q. Shi, Z.S. Lu, L.L. Mu and G.Y. Dai, *Synth. Commun*., 1998, **28** (6), 1073.
4 L.H. Zhou, S.J. Tu, D.Q. Shi and G.Y. Dai, *J. Chem. Res*., (S), 1998, 398.
5 L.H. Zhou, S.J. Tu, D.Q. Shi, G.Y. Dai and W.X. Chen, *Synthesis*, 1998, 851.
6 D.Q. Shi, J.X. Chen, W.Y. Chai, W.X. Chen and T.Y. Kao *Tetrahedron Lett*., 1993, **34**, 2963.
7 D.Q. Shi, L.L. Mu, Z.S. Lu and G.Y. Dai, *Synth. Commun*., 1997, **27**, 4121.
8 L.H. Zhou, D.Q. Shi, G.Y. Dai and W.X. Chen, *Tetrahedron Lett*., 1997, **38**, 2729.
9 D.Gravier, J.P. Dupin, F. Casadebaig, G. Hou, M. Boisseau and H. Bernard, *Pharmazie*, 1992, **47**, 91.
10 B.R. Baker, R.E. Schaub, J.P. Joseph, F.J. McEvoy and J.H. Williams, *J.Org. Chem*., 1953, **18**, 133.
11 J.F. Wolfe, T.L. Rathman, M.C. Sleevi, J.A. Campbell and T.D. Greenwood, *J. Med. Chem.*, 1990, **33**, 161.
12 M.T. Bogert and W.F. Hand, *J. Am. Chem., Soc*., 1902, **24**, 1032.
13 C. Bogentoft, L. Kronberg and B. Danielsson, *Acta. Pharm. Suec*., 1969, **6**, 485.
14 H. Stephen and G. Wadge, *J. Chem. Soc*., 1956, 4420.
15 H. Takeuchi, S. Haguvara and S. Eguchi, *Tetrahedron*, 1989, **45**, 6375.
16 H. Takeuchi, S. Haguvara and S. Eguchi, *J. Org. Chem.*, 1991, **56**, 1535.
17 S. Von Niementowski, *J. Prakt. Chem.*, 1895, **51**, 564.
18 P. Gotthelf and M.T. Bogert, *J. Am. Chem. Soc*., 1901, **23**, 611.
19 M.M. Endicott, E. Wick, M.L. Mercury and M. Sherrill, *J. Am. Chem. Soc*., 1946, **68**, 1299.
20 Y.M. Ma and Y.M. Zhang, *J. Chem. Res., (S)*, 2000, 388.
21 W.H. Zhang, Y.M. Zhang and X.Y. Chen, *Tetrahadron Lett.*, 2001, **42**, 73.
22 P.A. Petyunin and Y.V. Kozhevnikov, *Zh. Obshch. Khim*., 1960, **30**, 2352, *Chem. Abstr.*, 1961, **55**, 9402c.
23 C. Runtic, C. Nisi and L. Sindellari, *Ann. Chim.*, 1961, **51**, 719.