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Synthesis of quinazolin-4(3*H*)-ones and 1,2-dihydroquinazolin-4(3*H*)-ones with the aid of a low-valent titanium reagent

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Abstract—A short and facile synthesis of a series of quinazolin-4(3*H*)-ones and 1,2-dihydroquinazolin-4(3*H*)-ones was accomplished in good yields via the novel reductive cyclization of *o*-nitrobenzamides and triethyl orthoformate, aldehydes or ketones promoted by $TiCl_4$/Zn. © 2003 Published by Elsevier Science Ltd.

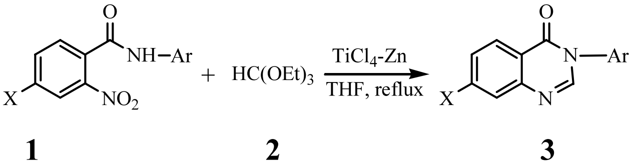
Low-valent titanium reagents have an exceedingly high ability to promote reductive coupling of carbonyl compounds and are attracting increasing interest in organic synthesis. Many other functional groups can also be coupled.[1]

Recently, we have reported the cyclodimerization of α,β-unsaturated ketones and α,β-unsaturated nitriles promoted by this reagent yielding functional cyclopentanes[2] and cyclopentenes,[3] respectively.

Preparations of quinazolin-4(3*H*)-ones are in demand because of their potential biological and pharmaceutical activities.[4] Unfortunately, synthetic methods for the elaboration of this bicyclic system 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[5] and the aza-Wittig reactions of α-azido-substituted aromatic imides.[6] Different one-pot syntheses 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.[7] Here we wish to describe a new method induced by the $TiCl_4$/Zn system for the preparation of quinazolin-4(3*H*)-ones and 1,2-dihydroquinazolin-4(3*H*)-ones using *o*-nitrobenzamides as the starting material.

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

Moreover, treatment of *o*-nitrobenzamides **4** and ketones or aromatic aldehydes **5** with $TiCl_4$–Zn in anhydrous THF under the same reaction conditions afforded 1,2-dihydroquinazolin-4(3*H*)-ones **6** in good yields (Scheme 2).



Scheme 1.

Table 1. The synthesis of quinazolin-4(3*H*)-ones promoted by $TiCl_4$/Zn

Entry	X	Ar	Isolated yield (%)
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

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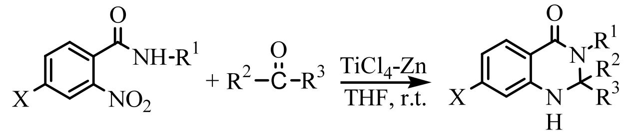
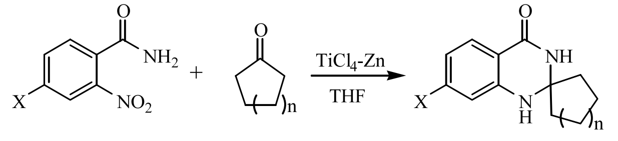


4 **5** **6**

Scheme 2.

Table 2 summarizes our results. All reactions could be carried out under mild conditions. However, *N*-phenyl-*o*-nitrobenzamide failed to react with 3-pentanone, cyclopentanone, benzaldehyde or acetophenone under these conditions, although the reaction of *o*-nitrobenzamide **4** and the cyclic ketones **7** with the same reagent system afforded 2,2-polymethylene-1,2-dihydroquinazolin-4(3*H*)-ones **8** (Scheme 3) and the results are summarized in Table 3. However, *o*-nitrobenzamide failed to react with acetophenone or 1-tetralone.

The structures of **3**, **6** and **8** were confirmed by IR, ^{1}H NMR and elemental analysis.[8] The structures of **3a** and **8c** were further confirmed by X-ray analysis (Fig. 1 and Fig. 2).[9]



4 **7** **8**

Scheme 3.

Table 3. The reductive cyclization of *o*-nitrobenzamides and cyclic ketones

Entry	X	*n*	Isolated yield (%)
8a	H	1	84
8b	Cl	1	89
8c	H	2	63
8d	Cl	2	83

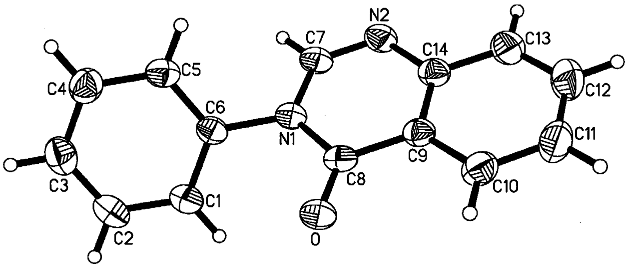


Figure 1. ORTEP diagram of **3a**.

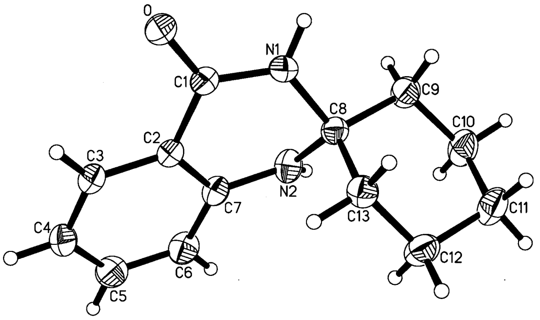


Figure 2. ORTEP diagram of **8c**.

In summary, a series of quinazolin-4(3*H*)-ones and 1,2-dihydroquinazolin-4(3*H*)-ones were synthesized via reductive cyclization of *o*-nitrobenzamides with triethyl orthoformate, aldehydes or ketones induced by the $TiCl_4$/Zn system. The advantages of our method are the easily accessible starting materials, convenient manipulation and moderate to high yields.

Table 2. The synthesis of 1,2-dihydroquinazolin-4(3*H*)-ones promoted by $TiCl_4$/Zn

Entry	X	R^1	R^2	R^3	Isolated yield (%)
6a	H	C_6H_5	CH_3	CH_3	81
6b	H	4-$CH_3C_6H_4$	CH_3	CH_3	88
6c	H	4-BrC_6H_4	CH_3	CH_3	83
6d	Cl	C_6H_5	CH_3	CH_3	85
6e	Cl	4-$CH_3C_6H_4$	CH_3	CH_3	89
6f	Cl	4-ClC_6H_4	CH_3	CH_3	86
6g	Cl	4-$CH_3C_6H_4$	CH_3	CH_3CH_2	79
6h	H	H	C_6H_5	H	82
6i	H	H	4-$CH_3C_6H_4$	H	91
6j	H	H	4-$CH_3OC_6H_4$	H	89
6k	H	H	4-ClC_6H_4	H	92
6l	H	H	3,4-$OCH_2OC_6H_3$	H	92
6m	H	H	3,4-$(OCH_3)_2C_6H_3$	H	93
6n	Cl	H	4-$CH_3C_6H_4$	H	80
6o	Cl	H	4-$CH_3OC_6H_4$	H	87

Acknowledgements

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8. Typical physical data for representative compounds: Compound **3a**, 3-phenylquinazolin-4(3*H*)-one mp 135–137°C (lit.[10] mp 138–139°C), ν_{max}: 3030, 1672, 1610, 1473, 1402, 1262, 1181, 1111, 1024, 933, 913, 767, 699, 623 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.43–7.46 (2H, m, ArH), 7.51–7.59 (4H, m, ArH), 7.77–7.85 (2H, m, ArH), 8.15 (1H, s, C_2-H), 8.38 (1H, d, $J=11$ Hz, C_5-H). Compound **6b**, 2,2-dimethyl-3-(4′-methylphenyl)-1,2-dihydroquinazolin-4(3*H*)-one mp 255–256°C, ν_{max}: 3306, 3025, 2978, 1627, 1519, 1399, 1277, 1176, 1108, 1022, 813, 755, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.49 (6H, s, 2×CH_3), 2.38 (3H, s, CH_3), 6.67–7.95 (8H, m, ArH). Anal. $C_{17}H_{18}N_2O$. Calcd C, 76.66; H, 6.81; N, 10.52. Found C, 76.83; H, 6.59; N, 10.63%. Compound **8c**, 2,2-penta-methylene-1,2-dihydroquinazolin-4(3*H*)-one mp 224–225°C, ν_{max}: 3367, 3109, 2924, 1652, 1484, 1382, 1270, 1178, 1145, 1040, 1004, 855, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.47–1.48 (2H, m, CH_2), 1.53–1.60 (4H, m, 2×CH_2), 1.83–1.84 (4H, m, 2×CH_2), 6.19 (1H, br., s, NH), 6.65–7.87 (4H, m, ArH). Anal. $C_{13}H_{16}N_2O$. Calcd C, 72.19; H, 7.46; N, 12.95. Found C, 72.32; H, 7.28; N, 13.15%.
9. X-Ray data for **3a** and **8c** have been deposited at the Cambridge Crystallographic Data Centre, deposition numbers CCDC 201812 and CCDC 201813. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Crystal data for **3a**: $C_{14}H_{10}N_2O$; M = 222.24, colorless block crystals, 0.50×0.50×0.24 mm, monoclinic, space group $P2_1/c$, $a=12.080(2)$, $b=7.7930(10)$, $c=11.5990(10)$ Å, $\beta=97.560(10)^\circ$, $V=1082.4(2)$ Å^3, $Z=4$, $D_C=1.364$ g cm^{-3}. $F(000)=464$, $\mu(\text{MoK}\alpha)=0.088$ mm^{-1}. Intensity data were collected on a Siemens P4 diffractometer with graphite monochromated MoKα radiation ($\lambda=0.71073$ Å) using the ω–2θ scan mode with $1.70^\circ<\theta<25.25^\circ$. 2312 unique reflections were measured and 1961 reflections with $I>2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final refinement was converged to $R=0.0358$ and $wR=0.0851$. Crystal data for **8c**: $C_{13}H_{16}N_2O$; M = 216.28, colorless block crystals, 0.52×0.48×0.44 mm, monoclinic, space group $P2_1/n$, $a=10.387(1)$, $b=10.954(2)$, $c=10.827(2)$ Å, $\beta=110.77(1)^\circ$, $V=1151.8(4)$ Å^3, $Z=4$, $D_C=1.247$ g cm^{-3}. $F(000)=464$, $\mu(\text{MoK}\alpha)=0.080$ mm^{-1}. Intensity data were collected on a Siemens P4 diffractometer with graphite-monochromated MoKα radiation ($\lambda=0.71073$ Å) using ω–2θ scan mode with $2.34^\circ<\theta<25.00^\circ$. 2033 unique reflections were measured and 1557 reflections with $I>2\sigma(I)$ were used in the structure refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final refinement was converged to $R=0.0449$ and $wR=0.1217$.
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