Copper-Catalyzed Domino Synthesis of Quinazolin-4(3*H*)-ones from (Hetero)arylmethyl Halides, Bromoacetate, and Cinnamyl Bromide

Haidong Wei,[a] Tianbin Li,[b] Yue Zhou,[a] Lihong Zhou,[a] Qingle Zeng*[a]

[a] Institute of Green Catalysis and Synthesis, College of Materials and Chemistry & Chemical Engineering, Chengdu University of Technology, Chengdu 610059, P. R. of China
Fax +86(28)84079074; E-mail: qinglezeng@hotmail.com

[b] State Key Lab of Geohazard Prevention and Geoenvironment Protection, Chengdu University of Technology, Chengdu 610059, P. R. of China

Received: 21.08.2013; Accepted after revision: 23.09.2013

Abstract: Alkyl halides, including heteroarylmethyl and arylmethyl halides, bromoacetate, and cinnamyl bromide, are readily prepared via halogenation from basic raw materials, even using green processes. It is essential to replace their downstream products with them to prepare medicinally important heterocycles quinazolin-4(3*H*)-ones. Copper(I) bromide catalyzed domino reaction of alkyl halides and anthranilamides under air affords 2-substituted quinazolin-4(3*H*)-ones in good to excellent yields and with wide functional group tolerance. A mechanism for a copper(I) bromide involved organometal-catalyzed reaction via a four-step domino reaction is proposed.

Key words: copper, condensation, tandem reaction, oxygenation, quinazolin-4(3*H*)-ones

2-Substituted quinazolin-4(3*H*)-ones are an important class of nitrogen-containing heterocycle that occur widely in natural products,[1] such as luotonin alkaloids[2] and rutaecarpine.[3] They have are of importance for their bioactivity and medical value,[1] e.g. for their anticancer,[4] anti-inflammatory,[5] antibacterial,[6] antihypertensive,[7] and antimalarial activity,[8] and as an antituberculosis agent,[9] vasopressin V3 receptor antagonist,[10] and nonpeptide cholecystokinin B receptor antagonist.[11]

The importance of 2-substituted quinazolin-4(3*H*)-ones promotes the development of methods for their synthesis.[1,2] These are commonly divided into two-component synthesis and three-component synthesis. In two-component synthesis, some typical pairs of two-component reactions are composed of: 2-aminobenzamides and benzoyl chlorides or their equivalents;[12] 2-halobenzoic acids or esters and arylamidines;[13] α-azido-substituted aromatic imides;[14] *o*-iodobenzamides and benzylamines;[15] anthranilamide and (hetero)aryl aldehydes;[16] anthranilamide and benzyl alcohols;[17] lithium 2-(diethylaminocarbonyl)anilide and (hetero)arylnitriles;[18] 2-aminobenzoic acids and benzimidates;[19] 1-aryl-4-(dimethylamino)-2-phenyl-1,3-diazabuta-1,3-dienes and phenyl isocyanate.[20] One of two components in each reaction, such as arylamidines, benzoyl chlorides, benzylamines, benzyl alcohols, and (hetero)arylnitriles, are downstream products of arylmethyl halides.

Generally, three-component condensation reactions are composed of isatoic anhydride, ammonium acetate (or amines), and benzaldehydes,[21] or composed of isatoic anhydride, orthoesters, and amines.[22] One of the three components is a benzaldehyde or an orthoester (i.e., (triethoxymethyl)benzene), which are also downstream products of arylmethyl halides.

The synthesis of 2-substituted quinazolin-4(3*H*)-ones using basic organic raw materials instead of their downstream products shortens the synthetic route, reduces environmental pollution, and lowers production costs, thus it is fundamental in industrial production and meaningful for academic research. Arylmethyl halides and heteroarylmethyl halides are readily prepared via halogenation from basic organic raw materials, methylarenes and heteromethylarenes,[23] even using green processes,[24] and thus a number of this type of chemicals are readily available and less expensive.

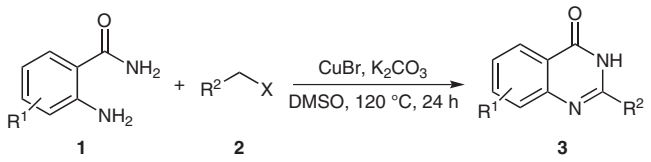
It is commonly known, and experimental results confirm, that anthranilamides are facilely benzylated with benzyl halides in the presence of the weak base potassium carbonate. Since *N*-benzylanilines can be oxidized into *N*-benzylideneanilines under 1 atm oxygen in the presence of cobalt Schiff base complex[25] or $Ru_2(OAc)_4Cl$,[26] then 2-(benzylamino)benzamide may be turned into 2-phenylquinazolin-4(3*H*)-ones under air in the presence of a suitable catalyst.

During the initial study, we found that copper(I) bromide directly transformed 2-(benzylamino)benzamide to 2-phenylquinazolin-4(3*H*)-ones under air at 120 °C. Further research showed that copper(I) bromide could directly turn anthranilamides and (hetero)arylmethyl halides into 2-(hetero)arylquinazolin-4(3*H*)-ones under air and in the presence of a weak base (Scheme 1).

As our ongoing research on synthesis of quinazolin-4(3*H*)-ones[16a] and transition-metal-catalyzed reactions,[27] we describe in this paper the copper(I) bromide catalyzed cascade synthesis of 2-(hetero)aryl-substituted quinazolin-4(3*H*)-ones from (hetero)arylmethyl halides and anthranilamides (Scheme 1).

SYNTHESIS 2013, 45, 3349–3354
Advanced online publication: 18.10.2013
DOI: 10.1055/s-0033-1340040; Art ID: SS-2013-F0579-OP
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: University of British Columbia. Copyrighted material.



Scheme 1 Copper-catalyzed domino synthesis of quinazolin-4(3*H*)-ones

To begin with, we took anthranilamide and benzyl bromide as the model substrates (Table 1). Considering that inexpensive and less toxic copper salts are both good oxidation catalysts with air as the oxidant[28] and based on our earlier study of copper(II) oxide as an efficient catalyst for the synthesis of quinazolin-4(3*H*)-ones,[16a] we initially chose copper(II) oxide as the catalyst to explore this new protocol.

When 5 mol% copper(II) oxide was examined, surprisingly 56% yield of the desired product 2-phenylquinazolin-4(3*H*)-one (**3a**) was obtained (entry 1). Further screening of various copper salts demonstrated that copper(I) bromide was the best catalyst for this cascade reaction (entries 1–6). 2-Phenylquinazolin-4(3*H*)-one (**3a**) was obtained in 89% yield in *N*,*N*-dimethylacetamide (DMA) under air atmosphere (entry 4), which means that oxygen in the air and copper(I) bromide fulfill the oxidation of the cascade reaction. Screening various bases (entries 7 and 8 vs. 4) and amounts (entries 9 and 10 vs. 4) did not give higher yields. Both shortening and prolonging the reaction time gave lower yields (entries 11 and 12 vs. 4). Investigation of the solvent indicates that dimethyl sulfoxide was better than *N*,*N*-dimethylacetamide and *N*,*N*-dimethylformamide (entries 4, 13, and 14). Lowering the amount of copper(I) bromide to 1 mol% caused a decrease in the

Table 1 Optimization of Conditions for the Reaction of Anthranilamide (**1a**) and Benzyl Bromide (**2a**)[a]

Entry	Catalyst (mol%)	Base	Solvent	Time (h)	Temp (°C)	Yield[b] (%) of **3a**
1	CuO (5)	K_2CO_3	DMA	24	120	56
2	Cu_2O (5)	K_2CO_3	DMA	24	120	66
3	CuI (5)	K_2CO_3	DMA	24	120	62
4	CuBr (5)	K_2CO_3	DMA	24	120	89
5	CuCl (5)	K_2CO_3	DMA	24	120	81
6	$CuCl_2$(5)	K_2CO_3	DMA	24	120	73
7	CuBr (5)	K_3PO_4	DMA	24	120	47
8	CuBr (5)	Cs_2CO_3	DMA	24	120	60
9[c]	CuBr (5)	K_2CO_3	DMA	24	120	66
10[d]	CuBr (5)	K_2CO_3	DMA	24	120	59
11	CuBr (5)	K_2CO_3	DMA	10	120	63
12	CuBr (5)	K_2CO_3	DMA	36	120	68
13	CuBr (5)	K_2CO_3	DMF	24	120	58
14	CuBr (5)	K_2CO_3	DMSO	24	120	93
15	CuBr (1)	K_2CO_3	DMSO	24	120	72
16	CuBr (2)	K_2CO_3	DMSO	24	120	97
17	CuBr (3)	K_2CO_3	DMSO	24	120	95
18	–[e]	K_2CO_3	DMSO	24	120	trace
19	CuBr (2)	K_2CO_3	DMSO	24	110	71
20	CuBr (2)	K_2CO_3	DMSO	24	130	79

[a] Reaction conditions: anthranilamide (1 mmol), BnBr (1 mmol), K_2CO_3 (1.0 equiv), copper source (0.02 equiv), solvent, temperature, time, unless otherwise mentioned.
[b] Isolated yield.
[c] K_2CO_3 (1.2 equiv).
[d] K_2CO_3 (0.8 equiv).
[e] No catalyst was added and the major product is 2-(benzylamino)benzamide (86% yield).

Downloaded by: University of British Columbia. Copyrighted material.

 © Georg Thieme Verlag Stuttgart · New York

yield (entries 14 vs. 15). Further screening of the amount of copper(I) bromide showed that 2 mol% afforded the highest yield of 97% (entries 14–17). The absence of copper(I) bromide in the reaction gave mainly 2-(benzylamino)benzamide and only trace amounts of the desired product (entry 18). Both increasing and lowering the temperature resulted in lower yields (entries 19 and 20).

With the optimized conditions in hand, we continued to investigate the reaction of (hetero)arylmethyl halides with anthranilamide (Table 2). 4-Methylbenzyl bromide gave a slightly higher yield for **3b** than the yield of **3a** from benzyl bromide (entries 2 vs. 1). The effect of the 2-, 3-, and 4-methyl-substitution on benzyl bromide produced marginal effects on their yields and **3b**–**d** were all obtained in excellent yields (entries 2–4). However, 2-fluorobenzyl bromide gave **3f** in about 10% lower yield than that the yield of **3e** from 3-fluorobenzyl bromide (entries 5 vs. 6). Moreover, the yield of **3g** from a 2,6-difluoro-substituted benzyl bromide sharply decreased (entries 7 vs. 6 and 5). Interestingly, 4-(trifluoromethyl)benzyl bromide and ethyl 4-(bromomethyl)benzoate gave **3j** and **3k**, respectively, in slightly lower yields (entries 10 and 11) and the electron-withdrawing or -donating properties of *p*- or *m*-substituted groups, such as fluoro, nitro, cyano, ethoxycarbonyl, methoxy, only slightly influenced the yields of **3e**,**h**,**i**,**l** (entries 5, 8, 9 vs. 12). It seems that ethyl 4-(4-oxo-3,4-dihydroquinazolin-2-yl)benzoate (**3k**) contains an ester group that was not hydrolyzed during the weak basic reaction conditions and the workup process (entry 11), and is an intermediate of a series of drug candidates with cytotoxic activities.[29]

Surprisingly, heteroaryl bromide, i.e., 2-(bromomethyl)pyridine afforded 2-(2-pyridyl)quinazolin-4(3*H*)-one (**3m**) (entry 13), a compound similar to a series of bioactive natural products luotonins,[2] rutaecarpine,[3] and drug candidates.[1a] Interestingly, 4-(chloromethyl)pyridine also gave the desired 2-(4-pyridyl)quinazolin-4(3*H*)-one (**3n**), whose derivative has a promising hypnotic effect,[30] but with a lower yield due to the lower reactivity of 4-(chloromethyl)pyridine (entry 14).

For 3-(trifluoromethyl)benzyl chloride, it seems that substitution of chloro or bromo group on benzyl position did not obviously affect the reactions (entries 15 vs. 10). However, benzyl chloride gave a much lower yield of **3a** than benzyl bromide due to its low reactivity (entries 16 vs. 1).

Table 2 Reactions of Heteroaryl- or Arylmethyl Halides **2** and Anthranilamide (**1a**, R^1 = H) (Scheme 1)[a]

Entry	R^2CH_2X **2**	X	R^2 in **3**	Product	Yield (%)
1	benzyl bromide	Br	Ph	**3a**	97
2	4-methylbenzyl bromide	Br	4-MeC_6H_4	**3b**	99
3	2-methylbenzyl bromide	Br	2-MeC_6H_4	**3c**	91
4	3-methylbenzyl bromide	Br	3-MeC_6H_4	**3d**	94
5	3-fluorobenzyl bromide	Br	3-FC_6H_4	**3e**	87
6	2-fluorobenzyl bromide	Br	2-FC_6H_4	**3f**	71
7	2,6-difluorobenzyl bromide	Br	2,6-$F_2C_6H_3$	**3g**	58
8	4-nitrobenzyl bromide	Br	4-$O_2NC_6H_4$	**3h**	89
9	3-cyanobenzyl bromide	Br	3-NCC_6H_4	**3i**	89
10	4-(trifluoromethyl)benzyl bromide	Br	4-$F_3CC_6H_4$	**3j**	75
11	ethyl 4-(bromomethyl)benzoate	Br	4-$EtO_2CC_6H_4$	**3k**	79
12	4-methoxybenzyl bromide	Br	4-$MeOC_6H_4$	**3l**	86
13	2-(bromomethyl)pyridine	Br	2-pyridyl	**3m**	80
14	4-(chloromethyl)pyridine	Cl	4-pyridyl	**3n**	55
15	3-(trifluoromethyl)benzyl chloride	Cl	3-$F_3CC_6H_4$	**3o**	71
16	benzyl chloride	Cl	Ph	**3a**	39
17	ethyl bromoacetate	Br	CO_2H	**3p**	77
18	cinnamyl bromide	Br	CH=CHPh	**3q**	79

[a] Reaction conditions: anthranilamide (1 mmol), benzyl bromide (1 mmol), K_2CO_3 (1.0 equiv), CuBr (0.02 equiv), DMSO, 120 °C, 24 h.

Downloaded by: University of British Columbia. Copyrighted material.

Interestingly, ethyl bromoacetate was able to react with anthranilamide to produce 4-oxo-3,4-dihydroquinazoline-2-carboxylic acid (**3p**), another valuable compound,[1] instead of 2-(ethoxycarbonyl)quinazolin-4(3*H*)-one.

Furthermore, cinnamyl bromide also reacted with anthranilamide and produced 2-styrylquinazolin-4(3*H*)-one (**3q**) (entry 18), whose derivatives are a class of antimitotic anticancer agents that inhibit tubulin polymerization,[4] and whose analogues containing pyridine structure are potent noncompetitive α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonists.[31] Moreover, 2-styrylquinazolin-4(3*H*)-one (**3q**) can be further transformed into a number of potential medicinal compounds.[1a]

Next we investigated the reaction of a few anthranilamides and arylmethyl bromides (Table 3). Reactions of 5-chloroanthranilamide and various arylmethyl bromides all gave good yields (entries 1 to 4). 3-Aminobenzofuran-2-carboxamide reacted with 3-methyl- and 3-fluorobenzyl bromides to afford the desired products **3v** and **3w**, respectively, (entries 5 and 6), which are promising candidates for use as medicines. Cascade reaction of 2-aminobenzanilide and arylmethyl bromides produced the 2,3-diarylquinazolin-4(3*H*)-ones **3x**,**y** in good yields (entries 7 and 8).

We propose a mechanism for copper(I) bromide catalyzed cascade reaction via S_N2 substitution of benzyl halides, aerobic oxidation of *N*-benzyl-substituted anthranilamides into *N*-benzylidene-substituted anthranilamides, intramolecular addition, and aerobic oxidation of 2-aryl-2,3-dihydroquinazolin-4(3*H*)-ones into 2-arylquinazolin-4(3*H*)-one. The plausible mechanism is depicted in Scheme 2.

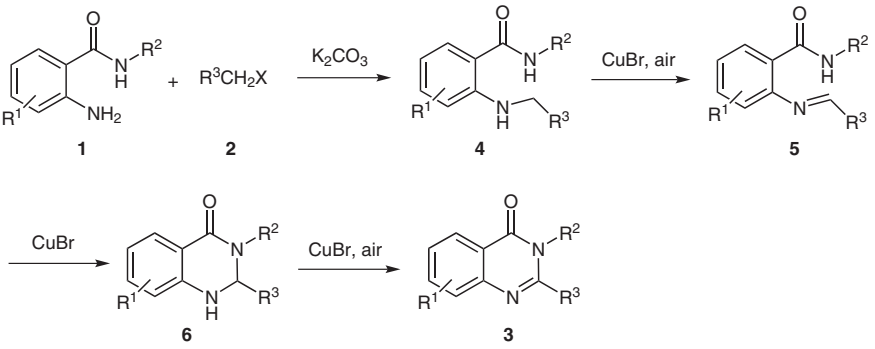
Under basic condition, S_N2 nucleophilic substitution of anthranilamide **1** and arylmethyl halide **2** (or ethyl bromoacetate, or cinnamyl bromide) occurs and produces 2-[(arylmethyl)amino]benzamide **4**, which was isolated and verified by NMR and could be transformed into the desired product under the same conditions. Next, compound **4** is oxidized by oxygen in the air under the catalysis of copper(I) bromide to produce *N*-arylmethylidene-substituted anthranilamide **5** due to its special structure. Intramolecular addition of the latter occurs promptly in the presence of copper(I) bromide to afford 2,3-dihydroquinazolin-4(3*H*)-one **6**. Compound **6** is oxidized under air atmosphere with the assistance of copper(I) bromide to afford the desired product, 2-arylquinazolin-4(3*H*)-one **3**.

In conclusion, copper(I) bromide catalyzed synthesis of 2-arylquinazolin-4(3*H*)-ones, a class of heterocycles with extensive pharmacological effects, from heteroarylmethyl

Table 3 Reactions of Anthranilamides **1** and Arylmethyl Bromides **2** (Scheme 2)[a]

Entry	Substrate	Arylmethyl bromide **2**	Product	Yield (%)
1	5-chloroanthranilamide	benzyl bromide	**3r**	87
2	5-chloroanthranilamide	2-fluorobenzyl bromide	**3s**	79
3	5-chloroanthranilamide	4-(trifluoromethyl)benzyl bromide	**3t**	82
4	5-chloroanthranilamide	4-methylbenzyl bromide	**3u**	75
5	3-aminobenzofuran-2-carboxamide	3-methylbenzyl bromide	**3v**	77
6	3-aminobenzofuran-2-carboxamide	3-fluorobenzyl bromide	**3w**	82
7	2-aminobenzanilide	benzyl bromide	**3x**	83
8	2-aminobenzanilide	4-methylbenzyl bromide	**3y**	89

[a] Reaction conditions: anthranilamide (1.0 mmol), benzyl bromide (1.0 mmol), K_2CO_3 (1.0 equiv), CuBr (0.02 equiv), DMSO, 120 °C, 24 h.



Scheme 2 A proposed mechanism

 © Georg Thieme Verlag Stuttgart · New York

Downloaded by: University of British Columbia. Copyrighted material.

or arylmethyl halides, ethyl bromoacetate, or cinnamyl bromide and anthranilamides via a one-pot cascade reaction has been developed. This process is inexpensive and simple, and it has a wide functional group tolerance. All bromides and partial halides examined (except 4-(chloromethyl)pyridine and benzyl chloride) afford good to excellent yields. A mechanism for the copper-catalyzed synthesis of 2-arylquinazolin-4(3*H*)-ones via a four-step cascade reaction containing S_N2 substitution, aerobic oxidation, addition, and aerobic oxidation was proposed.

Chemicals were purchased from Aldrich, Alfa Aesar, Acros, Aladdin, and Kelong Chemical Companies, and used without further purification. Reactions were monitored using TLC on commercial silica gel plates. Visualization of the developed plates was performed under UV light (254 nm). Flash column chromatography was performed on silica gel. The purity of all the synthesized compounds was checked by TLC using various combinations of non-aqueous organic solvents as eluent. Melting points were measured on an Electrothermal digital melting point apparatus without corrections. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 or 400 MHz spectrometer; referenced to internal TMS standard or the deuterated solvent $CDCl_3$, acetone-d_6, or DMSO-d_6. All IR spectra were taken on a Bruker Tensor-27 infrared spectrophotometer with an OPUS workstation. Combustion analyses are performed on a Euro EA-3000 elemental analyzer (Leeman Labs Inc.). Compounds **3a**,[16a] **3b**,[16a] **3c**,[32] **3d**,[32] **3e**,[18] **3f**,[18] **3g**,[33] **3h**,[34] **3j**,[18] **3l**,[34] **3m**,[35] **3n**,[13] **3o**,[18] **3p**,[36] **3q**,[37] **3r**,[16a] **3u**,[38] **3x**,[23] and **3y**[23] have been previously described in the literature.

2-Phenylquinazolin-4(3*H*)-one (3a) by Copper-Catalyzed Cascade Reaction of Anthranilamide (1a) and Benzyl Bromide (2a); Typical Procedure

To a 20-mL ground-in test tube equipped with a magnetic stirrer bar were added anthranilamide (1 mmol), CuBr (0.02 mmol), K_2CO_3 (1 mmol), DMSO (3 mL), and BnBr (1 mmol). The test tube was put in an oil bath preheated at 120 °C and kept stirring under air. After 24 h, the test tube was removed from the oil bath and cooled to r.t. The reaction was quenched with H_2O (2 mL) and then extracted with EtOAc (5 × 15 mL). The combined organic layer was washed with H_2O (2 × 10 mL) and dried (anhyd Na_2SO_4). The filtrate was condensed on a vacuum rotary evaporator. The residual was purified by column chromatography (silica gel, gradient petroleum ether–EtOAc) to give **3a** as a white solid; yield: 215.3 mg (97%).

3-(4-Oxo-3,4-dihydroquinazolin-2-yl)benzonitrile (3i)

White solid; yield 0.220 g (89%); mp 273–275 °C.

IR (KBr): 3419, 2396, 1677, 1619, 1472, 1315, 879, 771 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.75 (s, 1 H), 8.60 (s, 1 H), 8.49 (d, *J* = 7.7 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 7.86 (t, *J* = 7.4 Hz, 1 H), 7.82–7.72 (m, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.5, 151.3, 148.2, 136.6, 134.6, 132.5, 131.5, 129.9, 127.5 (C1′), 126.9, 125.9, 121.1, 118.3, 111.7, 108.9.

Anal. Calcd for $C_{15}H_9N_3O$: C, 72.87; H, 3.67; N, 16.99. Found: C, 72.62; H, 3.79; N, 16.72.

Ethyl 4-(4-Oxo-3,4-dihydroquinazolin-2-yl)benzoate (3k)

White solid; yield 0.232 g (79%); mp 279–281 °C.

IR (KBr): 3423, 2925, 2397, 2295, 1629 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.73 (s, 1 H), 8.31 (d, *J* = 8.0 Hz, 2 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 8.11 (s, 1 H), 7.89 (dd, *J* = 19.2, 8.0 Hz, 2 H), 7.82–7.72 (m, 1 H), 7.56 (t, *J* = 7.4 Hz, 1 H), 4.41–4.33 (m, 2 H), 1.34 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.1, 162.1, 148.5, 136.8, 134.7, 132.0, 129.1 (*J* = 24 Hz), 128.1, 127.6, 127.0, 126.2, 125.9, 121.1, 61.1, 14.1.

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.54; H, 4.53; N, 9.78.

6-Chloro-2-(2-fluorophenyl)quinazolin-4(3*H*)-one (3s)

White solid; yield 0.216 g (79%); mp 205–207 °C.

IR (KBr): 3420, 2071, 1635, 1389, 1084, 546 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.78 (s, 1 H), 8.11 (s, 1 H), 7.87–7.91 (m, 1 H), 7.75–7.80 (m, 2 H), 7.60–7.65 (m, 1 H), 7.35–7.43 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 160.5, 150.4, 147.4, 134.7, 133.1, 131.2, 131.0, 129.7 (*J* = 2 Hz), 124.7, 124.6, 124.5, 122.4, 116.3, 116.1.

Anal. Calcd for $C_{14}H_8ClFN_2O$: C, 61.22; H, 2.94; N, 10.20. Found: C, 61.50; H, 2.83; N, 10.12.

6-Chloro-2-[4-(trifluoromethyl)phenyl]quinazolin-4(3*H*)-one (3t)

White solid; yield 0.266 g (82%).

IR (KBr): 3412, 2084, 1675, 1638, 1469, 1393, 1324, 1184, 1121, 1085, 992, 946, 839, 550 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.94 (s, 1 H), 8.37 (d, *J* = 8.2 Hz, 2 H), 8.11 (d, *J* = 2.1 Hz, 1 H), 7.87–7.94 (m, 3 H), 7.80 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.4, 151.9, 147.2, 136.5, 134.7, 131.3, 131.2, 129.8, 128.8, 125.5 (*J* = 4 Hz), 125.3, 124.9, 122.5.

Anal. Calcd for $C_{15}H_8ClF_3N_2O$: C, 55.49; H, 2.48; N, 8.63. Found: C, 55.34; H, 2.68; N, 8.85.

2-(*m*-Tolyl)benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one (3v)

White solid; yield 0.213 g (77%); mp 291–293 °C.

IR (KBr): 3560, 2076, 1637, 1391, 1085, 991, 546 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.0 (s, 1 H), 8.12 (d, *J* = 7.7 Hz, 1 H), 7.93–7.99 (m, 2 H), 7.84 (d, *J* = 8.3 Hz, 1 H), 7.66–7.72 (m, 1 H), 7.52–7.54 (m, 1 H), 7.17–6.93 (m, 1 H), 2.42 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 156.3, 154.5, 153.4, 138.0 (*J* = 10 Hz), 131.9, 129.9, 129.1, 128.6 (*J* = 7 Hz), 128.1, 127.7, 125.4, 125.1, 124.4, 122.4, 121.4, 113.0, 20.9.

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.78; H, 4.71; N, 10.26.

2-(3-Fluorophenyl)benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one (3w)

White solid; yield 0.230 g (82%).

IR (KBr): 3499, 2075, 1637, 1391, 1086, 543 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.21 (s, 1 H), 8.14 (d, *J* = 7.5 Hz, 1 H), 8.11–7.94 (m, 2 H), 7.86 (t, *J* = 9.0 Hz, 1 H), 7.77–7.59 (m, 2 H), 7.60–7.33 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.3, 161.1, 160.8, 156.3, 153.2, 134.1, 130.8 (*J* = 8 Hz), 130.0, 124.5, 124.2 (*J* = 3 Hz), 122.3, 121.4, 118.2 (*J* = 21 Hz), 117.3, 114.8 (*J* = 24 Hz), 113.0.

Anal. Calcd for $C_{16}H_9FN_2O_2$: C, 68.57; H, 3.24; N, 10.00. Found: C, 68.69; H, 3.48; N, 9.87.

Downloaded by: University of British Columbia. Copyrighted material.

Acknowledgment

We appreciate the National Natural Science Foundation of China (No. 21372034), the Science and Technology Bureau of Sichuan (Grant No. 2011HH0016), the Incubation Program for Excellent Innovation Team of Chengdu University of Technology and the Opening Fund of State Key Laboratory of Geohazard Prevention and Geoenvironment Protection (No. SKLGP2012K005) for financial support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Eguchi, S. *Top. Heterocycl. Chem.* **2006**, *6*, 113. (b) Demeunynck, M.; Baussanne, I. *Curr. Med. Chem.* **2013**, *20*, 794.
(2) Liang, J. L.; Cha, H. C.; Jahng, Y. *Molecules* **2011**, *16*, 4861.
(3) Chen, A. L.; Chen, K. K. *J. Am. Pharm. Assoc.* **1933**, *22*, 716.
(4) Xia, Y.; Yang, Z. Y.; Hour, M. J.; Kuo, S. C.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoothiri, P.; Hackl, T.; Hamel, E.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1193.
(5) Alagarsamy, V.; Raja, S. V.; Dhanabal, K. *Bioorg. Med. Chem.* **2007**, *15*, 235.
(6) Selvam, P.; Girija, K.; Nagarajan, G.; De Clercq, E. *Indian J. Pharm. Sci.* **2005**, *67*, 484.
(7) Alagarsamy, V.; Pathak, U. S. *Bioorg. Med. Chem.* **2007**, *15*, 3457.
(8) Jang, C. S.; Fu, F. Y.; Wang, C. Y.; Huang, K. C.; Lu, G.; Thou, T. C. *Science (Washington, D.C.)* **1946**, *103*, 59.
(9) Kuneš, J.; Bažant, J.; Pour, M.; Waisser, K.; Šlosárek, M.; Janota, J. *Farmaco* **2000**, *55*, 725.
(10) Letourneau, J.; Riviello, C.; Ho, K.-K.; Chan, J.-H.; Ohlmeyer, M.; Jokiel, P.; Neagu, I.; Morphy, J. R.; Napier, S. E. WO 2006095014, **2006**.
(11) Padia, J. K.; Field, M.; Hinton, J.; Meecham, K.; Pablo, J.; Pinnock, R.; Roth, B. D.; Singh, L.; Suman-Chauhan, N.; Trivedi, B. K.; Webdale, L. *J. Med. Chem.* **1998**, *41*, 1042.
(12) Potewar, T. M.; Nadaf, R. N.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Synth. Commun.* **2005**, *35*, 231.
(13) Zhang, X.; Ye, D.; Sun, H.; Guo, D.; Wang, J.; Huang, H.; Zhang, X.; Jiang, H.; Liu, H. *Green Chem.* **2009**, *11*, 1881.
(14) Takeuchi, H.; Haguvara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375.
(15) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 1274.
(16) (a) Zhan, D.; Li, T.; Wei, H.; Weng, W.; Ghandi, K.; Zeng, Q. *RSC Adv.* **2013**, *3*, 9325. (b) Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. *Tetrahedron Lett.* **2004**, *45*, 3475.
(17) Zhou, J.; Fang, J. *J. Org. Chem.* **2011**, *76*, 7730.
(18) Couture, A.; Cornet, H.; Grandclaudon, P. *Synthesis* **1991**, 1009.
(19) Connolly, D. J.; Guiry, P. J. *Synlett* **2001**, 1707.
(20) Croce, P. D.; Ferraccioli, R.; La Rosa, C. *Heterocycles* **1997**, *45*, 1309.
(21) Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 3814.
(22) Mohammadi, A. A.; Sadat Hossini, S. S. *Chin. J. Chem.* **2011**, *29*, 1982.
(23) (a) Tanko, J. M.; Blackert, J. F. *Science (Washington, D.C.)* **1994**, *263*, 203. (b) Hunter, W. H.; Edgar, D. E. *J. Am. Chem. Soc.* **1932**, *54*, 2025.
(24) (a) Mestres, R.; Palenzuela, J. *Green Chem.* **2002**, *4*, 314. (b) Adimurthy, S.; Ghosh, S.; Patoliya, P. U.; Ramachandraiah, G.; Agrawal, M.; Gandhi, M. R.; Upadhyay, S. C.; Ghosh, P. K.; Ranu, B. C. *Green Chem.* **2008**, *10*, 232.
(25) Nishinaga, A.; Yamazaki, S.; Matsuura, T. *Tetrahedron Lett.* **1988**, *29*, 4115.
(26) Murahashi, S.-I.; Okano, Y.; Sato, H.; Nakae, T.; Komiya, N. *Synlett* **2007**, 1675.
(27) (a) Dong, J.; Wang, Y.; Xiang, Q.; Lv, X.; Weng, W.; Zeng, Q. *Adv. Synth. Catal.* **2013**, *355*, 692. (b) Dai, C.; Sun, X. F.; Tu, X. Z.; Wu, L.; Zhan, D.; Zeng, Q. *Chem. Commun.* **2012**, *48*, 5367. (c) Sun, X.; Tu, X.; Dai, C.; Zhang, X.; Zhang, B.; Zeng, Q. *J. Org. Chem.* **2012**, *77*, 4454. (d) Zeng, Q.; Gao, Y.; Dong, J.; Weng, W.; Zhao, Y. *Tetrahedron: Asymmetry* **2011**, *22*, 717.
(28) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science (Washington, D.C.)* **1996**, *274*, 2044.
(29) Rhee, H. K.; Yoo, J. H.; Lee, E.; Kwon, Y. J.; Lee, Y. S.; Choo, H.-Y. P.; Seo, H. R. *Eur. J. Med. Chem.* **2011**, *46*, 3900.
(30) Hisano, T.; Ichikawa, M.; Nakagawa, A.; Tsuji, M. *Chem. Pharm. Bull.* **1975**, *23*, 1910.
(31) Lazzaro, J. T.; Paternain, A. V.; Lerma, J.; Chenard, B. L.; Ewing, F. E.; Huang, J.; Welch, W. M.; Ganong, A. H.; Menniti, F. S. *Neuropharm* **2002**, *42*, 143.
(32) Ma, B.; Wang, Y.; Peng, J.; Zhu, Q. *J. Org. Chem.* **2011**, *76*, 6362.
(33) Chandrika, P. M.; Yakaiah, T.; Narsaiah, B.; Gayatri, G.; Kumar, K. P.; Murthy, U. S. N.; Rao, A. R. R. *Eur. J. Med. Chem.* **2010**, *45*, 78.
(34) Tavakoli-Hoseini, N.; Davoodnia, A. *Synth. React. Inorg., Met.-Org., Nano-Met. Chem.* **2012**, *42*, 76.
(35) Flanagan, S. P.; Goddard, R.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 9808.
(36) Baker, B. R.; Almaula, P. I. *J. Org. Chem.* **1962**, *27*, 4672.
(37) Trashakhova, T. V.; Nosova, E. V.; Valova, M. S.; Slepukhin, P. A.; Lipunova, G. N.; Charushin, V. N. *Russian J. Org. Chem.* **2011**, *47*, 753.
(38) El-Azab, A. S.; Al-Omar, M. A.; Abdel-Aziz, A. A.-M.; Abdel-Aziz, N. I.; El-Sayed, M. A.-A.; Aleisa, A. M.; Sayed-Ahmed, M. M.; Abdel-Hamide, S. G. *Eur. J. Med. Chem.* **2010**, *45*, 4188.

Downloaded by: University of British Columbia. Copyrighted material.

 © Georg Thieme Verlag Stuttgart · New York