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Copper-catalyzed three-component one-pot synthesis of quinazolines

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ABSTRACT

Two efficient approaches to multi-substituted quinazolines by the three-component one-pot reaction of *o*-bromo aromatic ketones/aldehydes, ammonia water and aromatic aldehydes, or primary alcohols catalyzed by CuCl have been developed.

1. Introduction

Quinazoline and its derivatives are important compounds found widespread in natural products and pharmaceuticals, which show interesting biological and physiological activities, such as antibacterial,[1] antiviral,[2] antitubercular,[3] and anticancer activities.[4] Therefore, a variety of synthetic methods have been developed to synthesize such type of compounds including microwave-promoted condensation of 2-aminoarylalkanone *o*-phenyl oximes with aldehydes,[5] condensation of 2-aminobenzophenone with benzylic amines,[6] condensation of 2-aminobenzylamines with aldehydes followed by subsequent oxidation with oxidants.[7] Recently, copper-catalyzed Ullmann *N*-arylations have made great progress, and which has been applied to develop the synthetic methods for quinazoline derivatives. For instance, copper-catalyzed condensation of *o*-halo-benzaldehydes with amidine hydrochlorides,[8] condensation of substituted (2-bromophenyl)-methylamines and amides under air via sequential Ullmann-type coupling and aerobic oxidation reaction.[9] However, all these above-mentioned procedures require nitrogen-containing starting materials, which are usually hard either to be available or to be pre-prepared. In the continuation of our interest in development of one-pot procedure to synthesize *N*-heterocyclic compounds using cheap and easily available starting materials,[10] in this paper, we report two protocols for the synthesis of multi-substituted quinazoline derivatives via CuCl-catalyzed one-pot, three-component cyclocondensation with the use of ammonia water as a source of nitrogen in the presence of oxidants.

2. Results and discussion

We initiated the study with the reaction of 2′-bromoacetophenone (**1a**), benzaldehyde (**2a**), and ammonia water to optimize the reaction conditions. As shown in Table 1, when a mixture of **1a** (0.50 mmol), **2a** (0.55 mmol), and ammonia water (25% aqueous ammonia, 1.0 mL) in NMP (0.5 mL) in a sealed tube under air was heated at 80 °C for 12 h, no desired product of 4-methyl-2-phenylquinazoline (**3a**) formed at all (entry 1) by the analyses of GC and GC–MS of the reaction mixture. Repeating the reaction in the presence of CuCl in toluene gave a trace amount of **3a** (entry 2), and in CH_3CN, DMSO and DMF, **3a** was obtained in fair yields (entries 3–5), in NMP, at 80 °C or 100 °C, the reaction afforded **3a** in good yields (entries 6–7). $CuCl_2$ also showed good catalytic activity for the formation of **3a** at 80 °C (entry 8). We screened other various copper(I) catalysts, such as CuI, CuBr and Cu_2O, and they showed slightly lower catalytic activity compared to CuCl (entries 9–11). Decreasing the reaction temperature to 60 °C or performing the reaction under nitrogen atmosphere led to significant decrease in catalytic activity of CuCl (entries 12–13). Therefore we investigated the scope of the present copper(I)-catalyzed three-component one-pot reaction with the use of various *o*-bromo aromatic aldehydes/

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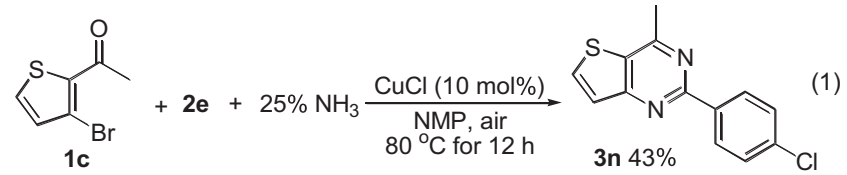
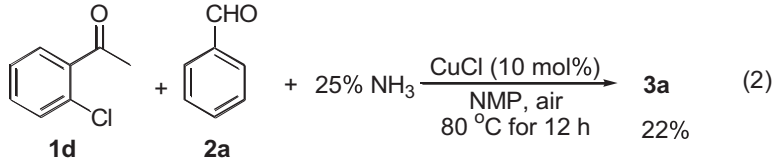
ketones, aromatic aldehydes, and ammonia water under the reaction conditions as indicated in entry 6.

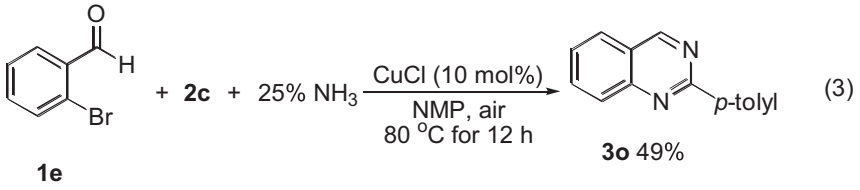
As summarized in Table 2, the cyclocondensation of **1a** and ammonia water with a variety of aryl aldehydes bearing electron-donating or -withdrawing groups yielded the desired quinazoline derivatives in fair to good yields, with an exception of 4-nitrobenzaldehyde used, which showed low reactivity and selectivity to form the corresponding quinazoline derivatives. In addition, the reaction of 2′-bromo-4′-fluoroacetophenone (**1b**) with both electron-donating and electron-withdrawing groups substituted aryl aldehydes occurred smoothly to afford the expected quinazoline derivatives in middle yields (37–51%).

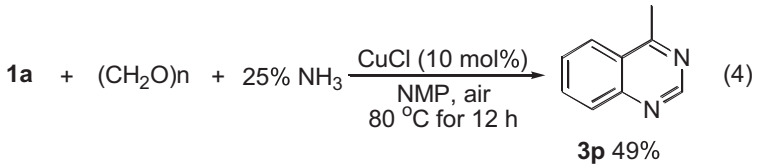
Furthermore, the reactions of 2-acetyl-3-bromothiophene (**1c**) with **2e** and ammonia water afforded the interesting both sulfur and nitrogen containing heterocyclic product of 2-(4-chlorophenyl)-4-methylthieno[3,2-*d*]pyrimidine (**3n**) in 43% isolated yield (Eq. 1). Notably, 2′-chloroacetophenone (**1d**) (Eq. 2) and 2-bromobenzaldehyde (**1e**) (Eq. 3) also underwent the present cyclocondensation, but relatively low yields were achieved compare to **1a** employed.

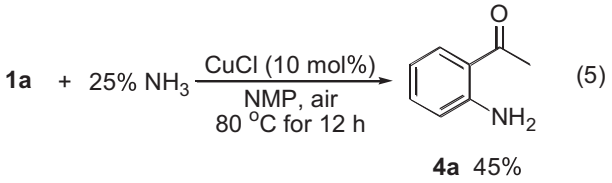
In the cases of aliphatic aldehydes used, unfortunately under the reaction conditions, aldol condensation of aliphatic aldehydes occurred predominantly for most cases, resulting in small amount of quinazoline derivatives, only the reaction of trioxane produced the corresponding 4-methylquinazoline (**3p**) in 49% yield (Eq. 4).



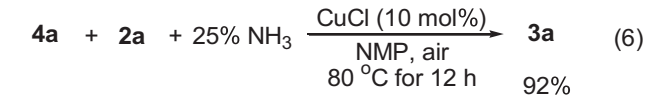


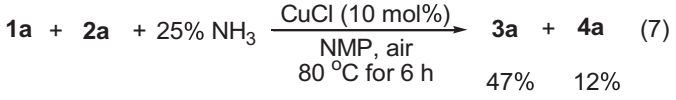






In order to elucidate the reaction mechanism for the formation of quinazoline derivatives, the following control experiments were performed. Firstly, the coupling reaction of (**1a**) (0.5 mmol) with 25% ammonia water (0.5 mL) in the presence of CuCl revealed that 2′-aminoacetophenone (**4a**) was formed in 45% yield (Eq. 5). Secondly, **4a** could be transformed into **3a** in 92% yield under the standard conditions (Eq. 6). Thirdly, if the reaction indicated in entry 6 of Table 1 was stopped in 6 h, both **3a** and **4a** could be isolated from the reaction mixture in 47% and 12% yield, respectively (Eq. 7). On the basis of these results, it is apparent that CuCl-catalyzed formation of **4a** in situ is the crucial intermediated for the formation of **3a**. Therefore, a proposed mechanism for the formation of quinazoline derivatives is shown in Scheme 1, it involves the Ullmann-type amination reaction of *o*-halo-acetophenones (**1**) with ammonia affording intermediate **4**, cyclocondensation of **4** with aldehydes and ammonia followed by aerobic oxidation reaction producing **3**.





As described above, under the standard reaction conditions, the reaction of 2′-bromoacetophenone, aliphatic aldehydes and ammonia water could not yield the expected quinazoline derivatives selectively due to the aldol condensation reaction. We assume that could be also applied to the reaction of **1a** or **1b**, ammonia water and various primary alcohols to afford quinazoline derivatives in fair to good yields (Table 4). It should be noted that the oxidation cyclocondensation procedure was efficient not only for benzyl alcohols to give 2-aryl substituted quinazoline derivatives, but also for aliphatic alcohols to produce 2-alkyl substituted quinazoline derivatives (**3o**, **3q**, **3r**, **3s** and **3v**), which should be more applicable to the synthesis of quinazoline derivatives.

In addition, the reaction of *o*-bromo benzyl alcohol, **5a** and ammonia water in the presence of DTBP (5.0 equiv) catalyzed by CuCl was also examined. As shown in Eq. 8, the expected product of 2-phenyl quinazolines (**3w**) was obtained in 16% isolated yield after 6 h, indicating that both *o*-bromobenzaldehyde and **2a** could be formed in situ, but it is a not efficient reaction system for the formation of 2-substituted quinazolines.

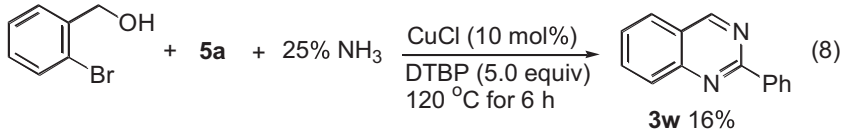
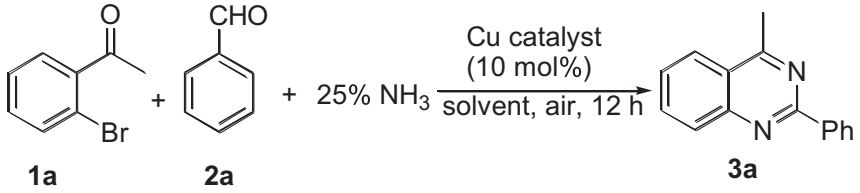


Table 1
Formation of 4-methyl-2-phenylquinazoline (**3a**) via the reaction of 2′-bromoacetophenone (**1a**), benzaldehyde (**2a**), and aqueous ammonia[a]



Entry	Catalyst	Solvent	Temp (°C)	Yield[b] (%)
1	—	NMP	80	0
2	CuCl	Toluene	80	<5
3	CuCl	Acetonitrile	80	32
4	CuCl	DMSO	80	32
5	CuCl	DMF	80	34
6	CuCl	NMP	80	65(63)
7	CuCl	NMP	100	66
8	$CuCl_2$	NMP	80	60
9	CuI	NMP	80	54
10	CuBr	NMP	80	58
11	Cu_2O	NMP	80	59
12	CuCl	NMP	60	43
13[c]	CuCl	NMP	80	22

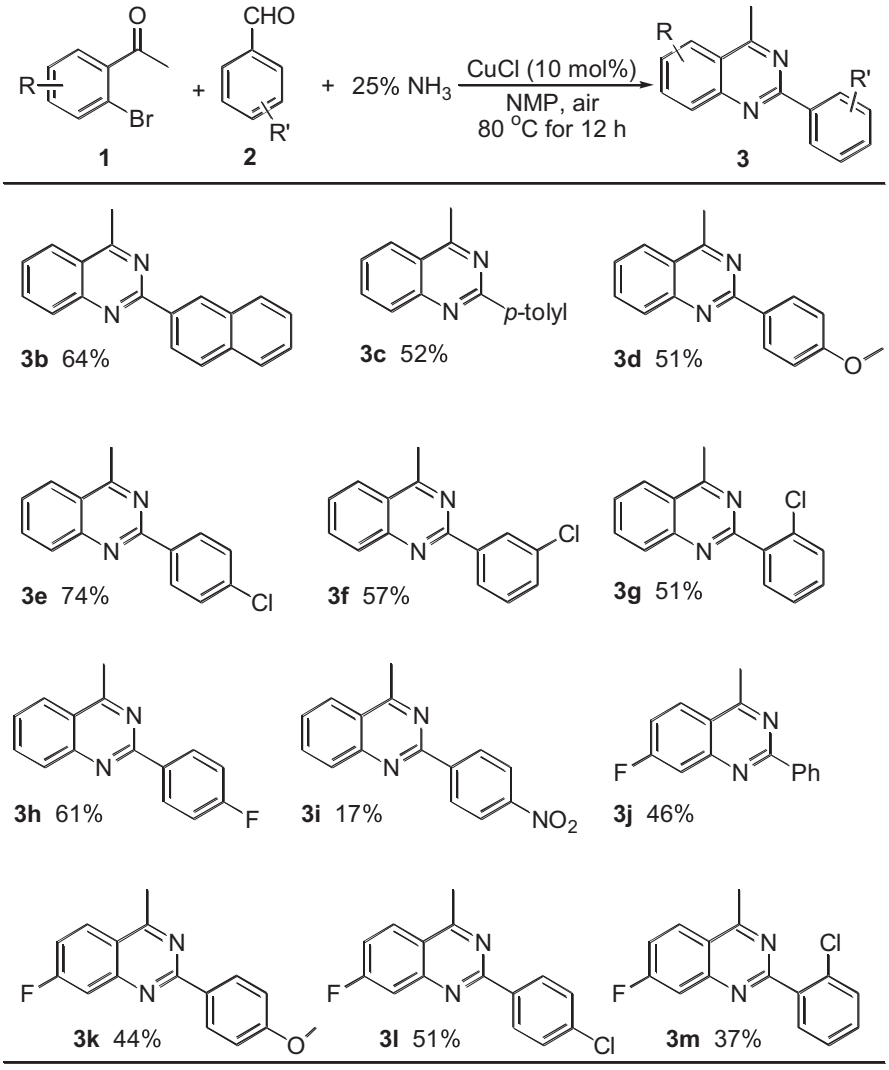
[a] Unless otherwise noted, the reactions were carried out with 0.5 mmol of **1a**, 0.55 mmol of **2a**, 0.5 mL of 25% aqueous ammonia, and 0.05 mmol of catalyst in 0.5 mL of solvent in a sealed tube under air for 12 h.
[b] GC yield based on the amount of **1a**. Number in parenthesis is isolated yield.
[c] Under nitrogen atmosphere.

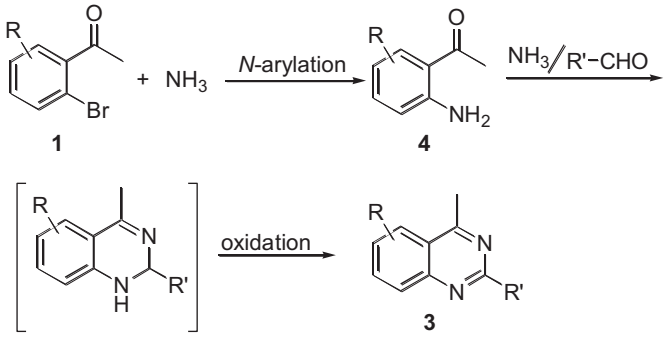
if the concentration of aliphatic aldehydes can be controlled in a low level, which might be the important factor to improve the formation of quinazolines. Therefore, we conducted an oxidation process of primary alcohol to aldehyde in the above-mentioned cyclocondensation. As shown in Table 3, we first examined the reaction of **1a**, benzyl alcohol (**5a**) and ammonia water under the similar reaction conditions as indicated in entry 6 of Table 1, in either NMP or without organic solvent, **3a** formed in 17% and 20% GC yield, respectively (Table 3, entries 1–2). Extremely encouraged by these results, we investigated the same reaction using 30% aqueous hydrogen peroxide and di-*tert*-butyl peroxide (DTBP) as oxidants under different reaction conditions, and it was found that when 2.5 equiv of DTBP was used, **3a** could be obtained in 66% GC yield at 120 °C for 6 h under organic solvent-free condition (Table 3, entry 6). Furthermore, this oxidation cyclocondensation procedure

3. Conclusions

In summary, we have developed the practical and efficient one-pot CuCl-catalyzed synthesis of multi-substituted quinazolines by the three-component reaction of either *o*-bromo aromatic ketones/aldehydes, aromatic aldehydes and ammonia water or *o*-bromo aromatic ketones/aldehydes, primary alcohols and ammonia water. The most significant features of the present catalytic systems include the use of easily accessible *o*-bromo aromatic aldehydes/ketones, aromatic aldehydes or primary alcohols, and ammonia water as starting materials, and air or DTBP (in the case of primary alcohols used) as the oxidants, as well as ammonia water as a source of nitrogen. The catalytic system with the use of primary alcohols as the precursor of aldehydes has more extensively applicable scope as both aryl and alkyl groups can be introduced at 2-position of quinazoline derivatives.

Table 2
Synthesis of quinazoline derivatives





Scheme 1. Proposed mechanism for CuCl-catalyzed formation of quinazolines.

4. Experimental section

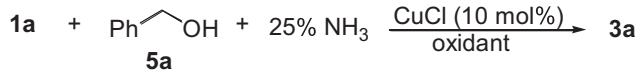
4.1. General methods

All organic starting materials are analytically pure and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on JOEL JNM-ECA300 spectrometers at 300 MHz and 75 MHz, respectively. ^{1}H NMR chemical shifts (δ) were referenced to TMS and ^{13}C NMR chemical shifts (δ) were referenced to internal solvent resonance. GC analyses of organic compounds were performed on an Agilent Technologies 1790 GC (with a TC-WAX capillary 25 m column) instrument. Mass spectra were obtained on a Shimadzu GC −MS-QP2010S, and HRMS was obtained on a micrOTOF-Q 10142.

4.2. Typical experimental procedure for condensation of 2′-bromoacetophenone (1a), benzaldehyde (2a), and ammonia water to afford 4-methyl-2-phenylquinazoline (3a) (Table 1, entry 6)

2′-Bromoacetophenone (**1a**) (100.0 mg, 0.5 mmol), benzaldehyde (**2a**) (58.0 mg, 0.55 mmol), CuCl (5.0 mg, 0.05 mmol), 25% aqueous ammonia (0.5 mL), and NMP (0.5 mL) were placed in a thick-walled Pyrex screw-cap tube (25 mL) under air atmosphere, and the tube was capped and the mixture was heated in an oil bath at 80 °C with stirring for 12 h. After the reaction mixture was cooled to room temperature, the crude reaction mixture was extracted with EtOAc for three times (3.0 mL×3). After removal of volatiles under a reduced pressure, the residue was diluted with CH_2Cl_2 (4.0 mL) and then *n*-docosane (62.1 mg, 0.2 mmol) was added as an internal standard for GC analysis. After GC and GC−MS analyses of the reaction mixture, volatiles were removed under a reduced pressure, and the residue was then subjected to silica gel column chromatography [eluting with petroleum ether and then with

Table 3
Formation of **3a** via the reaction of **1a**, benzyl alcohol (**5a**) and aqueous ammonia under different conditions[a]



Entry	Oxidant	Temp (°C)	Time (h)	Yield[b] (%)
1[c]	Air	80	18	17
2	Air	80	18	20
3	30% H_2O_2 (2.5 equiv)	80	12	30
4	30% H_2O_2 (2.5 equiv)	100	6	43
5	30% H_2O_2 (2.5 equiv)	120	6	53
6	DTBP (2.5 equiv)	120	6	66(65)
7	DTBP (5.0 equiv)	120	6	65
8	DTBP (1.0 equiv)	120	6	30
9[d]	DTBP (2.5 equiv)	120	6	65

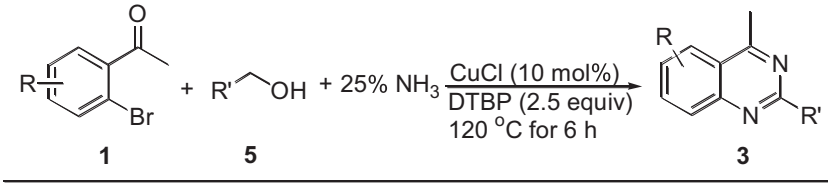
[a] Unless otherwise noted, the reactions were carried out with 0.5 mmol of **1a**, 1.5 mmol of **5a**, 0.5 mL of 25% aqueous ammonia and oxidant in a sealed tube under air for 12 h.
[b] GC yield based on the amount of **1a**. Number in parenthesis is isolated yield.
[c] NMP (0.5 mL) was used.
[d] Compound **5a** (2.5 mmol) was used.

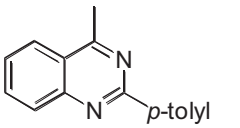
a mixture of petroleum ether and ethyl acetate (100:1–50:1)] to afford 4-methyl-2-phenylquinazoline (**3a**) (69.6 mg, 0.32 mmol, 63%) as white solid. The GC analysis of the reaction mixture disclosed the formation of **3a** in 65% GC yield.

4.3. Typical experimental procedure for condensation of 2′-bromoacetophenone (1a), benzyl alcohol (5a), and ammonia water to afford 4-methyl-2-phenylquinazoline (3a) (Table 3, entry 6)

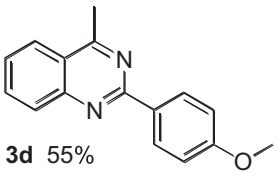
2′-Bromoacetophenone (**1a**) (100.0 mg, 0.5 mmol), benzyl alcohol (**5a**) (325.0 mg, 1.5 mmol), CuCl (5.0 mg, 0.05 mmol), DTBP (365.0 mg, 1.25 mmol), and 25% aqueous ammonia (0.5 mL) were placed in a thick-walled Pyrex screw-cap tube (25 mL), and the tube was capped and the mixture heated in an oil bath at 120 °C with stirring for 6 h. After the reaction mixture was cooled to room temperature, the work-up and isolation of the products were essentially similar to the procedure above-mentioned. Compound **3a** was obtained as white solid in 65% (71.5 mg, 0.33 mmol), and the GC analysis of the reaction mixture disclosed the formation of **3a** in 66% GC yield.

Table 4
Synthesis of quinazoline derivatives from primary alcohols

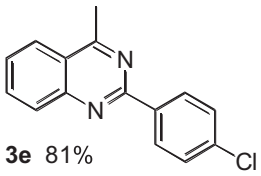




3c 62%



3d 55%



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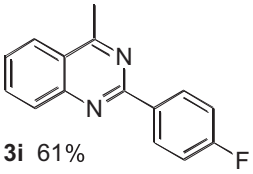
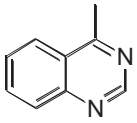


3i 61%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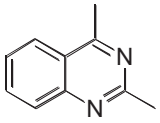
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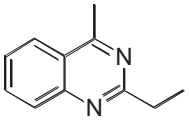
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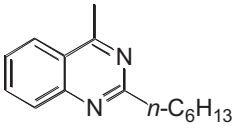

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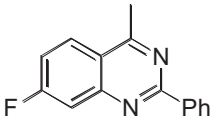

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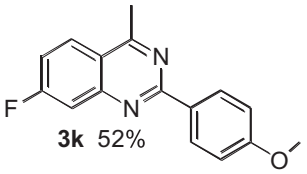

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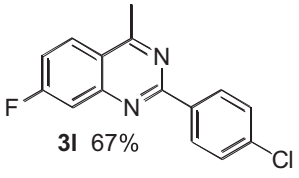

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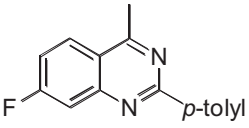

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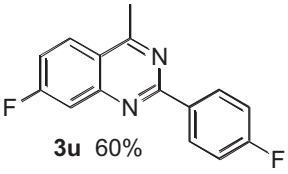

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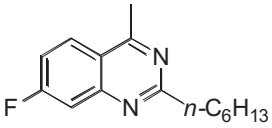

3v 53%

4.4. Characterization data for all products

*4.4.1. 4-Methyl-2-phenylquinazoline (**3a**).*[11] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, J=7.6, 1.7 Hz, 2H), 7.98 (d, J=8.6 Hz, 1H), 7.87 (dt, J=8.3, 0.7 Hz, 1H), 7.71 (t, J=7.6 Hz, 1H), 7.52–7.37 (m, 4H), 2.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 160.0, 150.2, 138.3, 133.3, 130.3, 129.1, 128.5, 128.4, 126.7, 124.8, 122.8, 21.9; GC–MS m/z (% rel inten.) 220 (M^+, 100), 205 (56), 179 (34).

*4.4.2. 4-Methyl-2-(naphthalen-2-yl)quinazoline (**3b**).* Yellow solid; mp 122.0–123.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.73 (dd, J=8.6, 1.4 Hz, 1H), 8.09 (d, J=8.6 Hz, 1H), 8.05–8.01 (m, 2H), 7.96 (d, J=8.6 Hz, 1H), 7.91–7.80 (m, 2H), 7.57–7.48 (m, 3H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 160.2, 150.5, 135.8, 134.7, 133.6, 133.5, 129.4, 129.3, 128.9, 128.3, 127.8, 127.1, 127.0, 126.2, 125.6, 125.1, 123.1, 22.1; GC–MS m/z (% rel inten.) 270 (M^+, 100), 255 (34), 127 (28); HRMS (ESI): calcd for $C_{19}H_{15}N_2$ $[M+H]^+$: 271.1230; found: 271.1225.

*4.4.3. 4-Methyl-2-p-tolylquinazoline (**3c**).* Yellow solid; mp 99.0–101.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J=7.9 Hz, 2H), 8.03–7.93 (m, 2H), 7.77 (ddd, J=8.4, 7.0, 1.4 Hz, 1H), 7.49–7.42 (m, 1H), 7.30 (d, J=7.9 Hz, 2H), 2.92 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 160.2, 150.4, 140.6, 135.6, 133.4, 129.3, 129.1, 128.5, 126.6, 125.0, 122.9, 22.0, 21.6; GC–MS m/z (% rel inten.) 234 (M^+, 100), 219 (43), 91 (16); HRMS (ESI): calcd for $C_{16}H_{15}N_2$ $[M+H]^+$: 235.1230; found: 235.1240.

*4.4.4. 2-(4-Methoxyphenyl)-4-methylquinazoline (**3d**).*[11] Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J=8.9 Hz, 2H), 8.11–7.96 (m, 2H), 7.88–7.75 (m, 1H), 7.58–7.45 (m, 1H), 7.02 (d, J=8.9 Hz, 2H), 3.87 (s, 3H), 2.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 161.7, 159.9, 150.5, 133.5, 131.0, 130.2, 129.0, 126.4, 125.0, 122.7, 113.9, 55.4, 22.1; GC–MS m/z (% rel inten.) 250 (M^+, 100), 235 (48), 209 (9).

*4.4.5. 2-(4-Chlorophenyl)-4-methylquinazoline (**3e**).*[11] Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J=8.3 Hz, 2H), 7.94 (t, J=8.9 Hz, 2H), 7.76 (t, J=7.7 Hz, 1H), 7.52–7.38 (m, 3H), 2.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 158.9, 150.1, 136.7, 136.5, 133.6, 129.9, 129.1, 128.7, 127.0, 124.9, 122.9, 22.0; GC–MS m/z (% rel inten.) 256 (34), 254 (M^+, 100), 239 (45), 213 (18), 102 (22), 76 (21).

*4.4.6. 2-(3-Chlorophenyl)-4-methylquinazoline (**3f**).* Yellow solid; mp 100.8–101.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.52–8.48 (m, 1H), 8.09–8.02 (m, 2H), 7.85 (t, J=7.6 Hz, 1H), 7.58 (t, J=7.6 Hz, 1H), 7.46–7.41 (m, 2H), 2.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 158.9, 150.3, 140.2, 134.8, 133.8, 130.4, 129.9, 129.4, 128.7, 127.3, 126.7, 125.1, 123.2, 22.1; GC–MS m/z (% rel inten.) 256 (32), 254 (M^+, 100), 239 (42), 76 (24); HRMS (ESI): calcd for $C_{15}H_{12}ClN_2$ $[M+H]^+$: 255.0684; found: 255.0694.

*4.4.7. 2-(2-Chlorophenyl)-4-methylquinazoline (**3g**).* Yellow solid; mp 110.3–111.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20–8.10 (m, 2H), 7.97–7.89 (m, 1H), 7.81–7.76 (m, 1H), 7.72–7.65 (m, 1H), 7.55–7.50 (m, 1H), 7.43–7.37 (m, 2H), 3.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 161.3, 150.0, 138.7, 134.0, 132.9, 131.6, 130.6, 130.2, 129.3, 127.8, 127.0, 125.1, 122.8, 22.0; GC–MS m/z (% rel inten.) 256 (18), 254 (M^+, 56), 239 (35), 219 (100), 76 (28); HRMS (ESI): calcd for $C_{15}H_{12}ClN_2$ $[M+H]^+$: 255.0684; found: 255.0685.

*4.4.8. 2-(4-Fluorophenyl)-4-methylquinazoline (**3h**).*[11] Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69–8.56 (m, 2H), 8.10–8.00 (m, 2H), 7.83 (ddd, J=8.3, 7.0, 1.2 Hz, 1H), 7.55 (ddd, J=8.3, 6.9, 1.1 Hz, 1H), 7.22–7.14 (m, 2H), 2.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 164.7 (d, J^1C–F=250.0 Hz), 159.3, 150.5, 134.6 (d, J^4C–F=2.2 Hz), 133.7, 130.7 (d, J^3C–F=8.0 Hz), 129.2, 127.0, 125.1, 123.0, 115.5 (d, J^2C–F=21.7 Hz), 22.1; GC–MS m/z (% rel inten.) 238 (M^+, 100), 223 (57), 197 (34), 76 (23).

*4.4.9. 4-Methyl-2-(4-nitrophenyl)quinazoline (**3i**).*[5b] Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (dt, J=8.9, 2.1 Hz, 2H), 8.29 (dt, J=8.9, 2.1 Hz, 2H), 8.07 (t, J=8.1 Hz, 2H), 7.89 (ddd, J=8.3, 6.9, 1.2 Hz, 1H), 7.63 (ddd, J=8.2, 6.9, 1.1, 1H), 3.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 157.9, 150.2, 149.1, 144.2, 134.1, 129.5, 129.4, 128.0, 125.2, 123.7, 123.3, 22.1; GC–MS m/z (% rel inten.) 265 (M^+, 100), 219 (62).

*4.4.10. 7-Fluoro-4-methyl-2-phenylquinazoline (**3j**).* Yellow solid; mp 69.5–71.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63–8.56 (m, 2H), 8.05–8.00 (m, 1H), 7.63 (dd, J=10.0, 2.4 Hz, 1H), 7.54–7.48 (m, 3H), 7.32–7.24 (m, 1H), 2.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 165.6 (d, J^1C–F=254.3 Hz), 161.2, 152.4 (d, J^3C–F=13.7 Hz), 138.0, 130.8, 128.8, 128.7, 127.7 (d, J^3C–F=10.8 Hz), 120.3, 117.2 (d, J^2C–F=25.3 Hz), 112.9 (d, J^2C–F=20.2 Hz), 22.2; GC–MS m/z (% rel inten.) 238 (M^+, 100), 223 (51), 197 (29), 77 (33); HRMS (ESI): calcd for $C_{15}H_{12}FN_2$ $[M+H]^+$: 239.0979; found: 239.0981.

*4.4.11. 7-Fluoro-2-(4-methoxyphenyl)-4-methylquinazoline (**3k**).* Yellow solid; mp 134.5–136.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J=8.9 Hz, 2H), 8.04 (dd, J=8.9, 5.9 Hz, 1H), 7.64–7.59 (m, 1H), 7.32–7.23 (m, 1H), 7.02 (d, J=8.9 Hz, 2H), 3.89 (s, 3H), 2.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 165.6 (d, J^1C–F=254.3 Hz), 162.0, 161.0, 152.5 (d, J^3C–F=13.7 Hz), 130.7, 130.4, 127.7 (d, J^3C–F=10.8 Hz), 120.1, 116.7 (d, J^2C–F=25.3), 114.0, 112.7 (d, J^2C–F=20.2 Hz), 55.5, 22.2; GC–MS m/z (% rel inten.) 268 (M^+, 100), 253 (46), 227 (6); HRMS (ESI): calcd for $C_{16}H_{14}FN_2O$ $[M+H]^+$: 269.1085; found: 269.1085.

*4.4.12. 2-(4-Chlorophenyl)-7-fluoro-4-methylquinazoline (**3l**).* Yellow solid; mp 158.8–160.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J=8.6 Hz, 2H), 8.06 (dd, J=8.9, 6.0 Hz, 1H), 7.62 (dd, J=10.0, 2.4 Hz, 1H), 7.46 (d, J=8.6 Hz, 2H), 7.32 (dt, J=8.7, 2.4 Hz, 1H), 2.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 165.7 (d, J^1C–F=255.0 Hz), 160.2, 152.3 (d, J^3C–F=13.7 Hz), 137.0, 136.5, 130.1, 128.9, 127.8 (d, J^3C–F=10.1 Hz), 120.4, 117.4 (d, J^2C–F=25.3 Hz), 113.0 (d, J^2C–F=20.2 Hz), 22.2; GC–MS m/z (% rel inten.) 274 (35), 272 (M^+, 100), 257 (46), 111 (19); HRMS (ESI): calcd for $C_{15}H_{11}ClFN_2$ $[M+H]^+$: 273.0589; found: 273.0596.

*4.4.13. 2-(2-Chlorophenyl)-7-fluoro-4-methylquinazoline (**3m**).* Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (dd, J=9.1, 6.0 Hz, 1H), 7.80–7.76 (m, 1H), 7.72 (dd, J=9.6, 2.8 Hz, 1H), 7.55–7.50 (m, 1H), 7.47–7.37 (m, 3H), 3.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 165.8 (d, J^1C–F=256.5 Hz), 162.4, 152.0 (d, J^3C–F=13.7 Hz), 138.4, 133.0, 131.6, 130.7, 130.5, 127.9 (d, J^3C–F=10.1 Hz), 127.0, 120.1, 118.2 (d, J^2C–F=25.3 Hz), 113.1 (d, J^2C–F=20.2 Hz), 22.1; GC–MS m/z (% rel inten.) 274 (14), 272 (M^+, 44), 257 (24), 237 (100); HRMS (ESI): calcd for $C_{15}H_{11}ClFN_2$ $[M+H]^+$: 273.0589; found: 273.0594.

*4.4.14. 2-(4-Chlorophenyl)-4-methylthieno[3,2-d]pyrimidine (**3n**).* White solid; mp 142.6–143.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J=8.6 Hz, 2H), 7.92 (d, J=5.5 Hz, 1H), 7.55 (d, J=5.5 Hz, 1H), 7.45 (d, J=8.6 Hz, 2H), 2.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.4, 160.3, 136.8, 136.4, 135.1, 129.7, 128.8, 125.2, 23.6; GC–MS m/z (% rel inten.) 262 (39), 260 (M^+, 100), 245 (32), 111 (22); HRMS (ESI): calcd for $C_{13}H_{10}ClN_2S$ $[M+H]^+$: 261.0248; found: 261.0250.

*4.4.15. 2-p-Tolylquinazoline (**3o**).*[9] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.51 (d, J=8.3 Hz, 2H), 8.08–8.03 (m, 1H), 7.91–7.82 (m, 2H), 7.55 (ddd, J=7.9, 6.9, 1.0 Hz, 1H), 7.22 (d, J=7.9 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 160.5, 150.9,

141.0, 135.4, 134.1, 129.5, 128.6, 127.2, 127.1, 123.6, 21.6; GC–MS *m*/*z* (% rel inten.) 220 (M^+, 100), 219 (31), 193 (21), 91 (11), 76 (11).

*4.4.16. 4-Methylquinazolin (**3p**).*[11] Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.10 (d, *J*=8.6 Hz, 1H), 8.03 (d, *J*=8.6 Hz, 1H), 7.92–7.85 (m, 1H), 7.68–7.61 (m, 1H), 2.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 154.6, 149.6, 133.7, 129.1, 127.6, 125.1, 124.6, 21.9; GC–MS *m*/*z* (% rel inten.) 144 (M^+, 100), 129 (26), 103 (33), 76 (34).

*4.4.17. 2,4-Dimethylquinazoline (**3q**).*[8a] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J*=8.3 Hz, 1H), 7.92 (d, *J*=8.3 Hz, 1H), 7.83 (ddd, *J*=8.3, 6.9, 1.4 Hz, 1H), 7.55 (ddd, *J*=8.3, 6.9, 1.0 Hz, 1H), 2.91 (s, 3H), 2.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 163.5, 149.8, 133.6, 128.2, 126.6, 124.9, 122.2, 26.4, 21.7; GC–MS *m*/*z* (% rel inten.) 158 (M^+, 100), 143 (59), 117 (47), 76 (19).

*4.4.18. 2-Ethyl-4-methylquinazoline (**3r**).* Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J*=8.3 Hz, 1H), 7.96 (d, *J*=8.3 Hz, 1H), 7.83 (t, *J*=7.5 Hz, 1H), 7.56 (t, *J*=7.5 Hz, 1H), 3.10 (q, *J*=7.6 Hz, 2H), 2.93 (s, 3H), 1.46 (t, 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 167.8, 150.0, 133.5, 128.5, 126.6, 125.0, 122.5, 33.3, 21.9, 13.2; GC–MS *m*/*z* (% rel inten.) 172 (M^+, 65), 171 (100), 144 (19), 129 (14), 76 (11); HRMS (ESI): calcd for $C_{11}H_{13}N_2$ $[M+H]^+$: 173.1073; found: 173.1072.

*4.4.19. 2-Hexyl-4-methylquinazoline (**3s**).* Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J*=8.3 Hz, 1H), 7.96 (d, *J*=8.3 Hz, 1H), 7.87–7.80 (m, 1H), 7.56 (t, *J*=7.4 Hz, 1H), 3.05 (t, *J*=7.9 Hz, 2H), 2.93 (s, 3H), 1.95–1.84 (m, 2H), 1.50–1.27 (m, 6H), 0.88 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 167.2, 150.0, 133.6, 128.5, 126.6, 125.0, 122.5, 40.3, 31.9, 29.5, 29.3, 22.7, 21.9, 14.2; GC–MS *m*/*z* (% rel inten.) 228 (M^+, 9), 185 (14), 171 (29), 158 (100), 117 (8); HRMS (ESI): calcd for $C_{15}H_{21}N_2$ $[M+H]^+$: 229.1699; found: 229.1695.

*4.4.20. 7-Fluoro-4-methyl-2-p-tolylquinazoline (**3t**).* Yellow solid; mp 77.8–78.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, *J*=8.5 Hz, 2H), 8.05 (dd, *J*=8.8, 5.9 Hz, 1H), 7.64 (dd, *J*=9.8, 2.4 Hz, 1H), 7.34–7.28 (m, 3H), 2.96 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 165.5 (d, J^1C–F=254.3 Hz), 161.2, 152.3 (d, J^3C–F=13.7 Hz), 141.0, 135.2, 129.4, 128.7, 127.7 (d, J^3C–F=10.8 Hz), 120.2, 116.9 (d, J^2C–F=25.3 Hz), 112.8 (d, J^2C–F=20.2 Hz), 22.2, 21.6; GC–MS *m*/*z* (% rel inten.) 252 (M^+, 100), 237 (38), 211 (12), 91 (18); HRMS (ESI): calcd for chemical formula: $C_{16}H_{14}FN_2$ $[M+H]^+$: 253.1136; found: 253.1130.

*4.4.21. 7-Fluoro-2-(4-fluorophenyl)-4-methylquinazoline (**3u**).* Yellow solid; mp 147.4–148.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63–8.56 (m, 2H), 8.05 (dd, *J*=9.4, 5.9 Hz, 1H), 7.61 (dd, *J*=9.6, 2.8 Hz, 1H), 7.34–7.26 (m, 1H), 7.21–7.14 (m, 2H), 2.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 165.6 (d, J^1C–F=255.0 Hz), 164.8 (d, J^1C–F=250.0 Hz), 160.2, 152.3 (d, J^3C–F=13.7 Hz), 134.1 (d, J^4C–F=2.9 Hz), 130.9 (d, J^3C–F=8.7 Hz), 127.8 (d, J^3C–F=10.1 Hz), 120.2, 117.2 (d, J^2C–F=24.6 Hz), 115.6 (d, J^2C–F=21.7 Hz), 112.9 (d, J^2C–F=19.5 Hz), 22.2; GC–MS *m*/*z* (% rel inten.) 256 (M^+, 100), 241 (55), 215 (32), 95 (27), 75 (10); HRMS (ESI): calcd for $C_{15}H_{11}F_2N_2$ $[M+H]^+$: 257.0855; found: 257.0889.

*4.4.22. 7-Fluoro-2-hexyl-4-methylquinazoline (**3v**).* Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, *J*=9.5, 5.9 Hz, 1H), 7.56 (dd, *J*=9.6, 2.4 Hz, 1H), 7.31 (dt, *J*=8.6, 2.4 Hz, 1H), 3.03 (t, *J*=7.9 Hz, 2H), 2.91 (s, 3H), 1.94–1.83 (m, 2H), 1.47–1.28 (m, 6H), 0.88 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 167.8, 165.5 (d, J^1C–F=254.3 Hz), 151.9 (d, J^3C–F=13.7 Hz), 127.7 (d, J^3C–F=10.8 Hz), 119.8, 116.9 (d, J^2C–F=24.6 Hz), 112.3 (d, J^2C–F=20.2 Hz), 40.2, 31.8, 29.4, 29.1, 22.7, 21.9, 14.2; GC–MS *m*/*z* (% rel inten.) 246 (M^+, 9), 203 (14), 189 (29), 176 (100), 161 (7); HRMS (ESI): calcd for $C_{15}H_{20}FN_2$ $[M+H]^+$: 247.1605; found: 247.1610.

*4.4.23. 2-Phenyl quinazoline (**3w**).*[8a] Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.62 (d, *J*=6.9 Hz, 2H), 8.08 (d, *J*=8.3 Hz, 1H), 7.92–7.87 (m, 2H), 7.59 (t, *J*=7.2 Hz, 1H), 7.54–7.51 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.2, 160.6, 150.9, 138.2, 134.2, 130.7, 128.9, 128.8, 128.7, 127.4, 127.2, 123.7; GC–MS *m*/z (% rel inten.) 206 (M^+, 100), 179 (56), 103 (34), 76 (53).

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Supplementary data

Copies of ^{1}H, and ^{13}C NMR charts for all products are included in Supplementary data. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.035.

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