Tetrahedron 71 (2015) 419–423

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

New efficient synthesis of 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-diones via a tandem aza-Wittig/nucleophilic addition/intramolecular cyclization/isomerization reaction starting from the Baylis–Hillman adducts

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ARTICLE INFO

Article history:
Received 14 October 2014
Received in revised form 26 November 2014
Accepted 1 December 2014
Available online 5 December 2014

Keywords:
1*H*-Pyrimido[2,1-*b*]quinazoline-2,6-dione
Aza-Wittig reaction
Baylis–Hillman reaction
Nucleophilic addition
Isomerization

ABSTRACT

Iminophosphoranes **3**, obtained from the Baylis–Hillman adducts, reacted with 2-azidobenzoyl chloride to give the azides **4**. The sequential reaction of azides **4** with triphenylphosphine and isocyanate produced 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-diones **9** in the presence of sodium ethoxide via a tandem aza-Wittig/nucleophilic addition/intramolecular cyclization/isomerization reaction.

1. Introduction

The synthesis of quinazolinones has been the focus of continuing interest because these ring systems lie at the heart of a great number of biologically active poly- and diversely functionalized compounds. For example, some of the quinazolinones have been found to show antimicrobial,[1] antiinflammatory,[2] antifungal,[3] anticancer,[4] anticonvulsant,[5] tankyrase inhibitive,[6] phosphatidylinositol 4-kinase α (PI4KIIIα) inhibitive,[7] and histone deacetylase-6 inhibitive activities.[8] In addition, quinazolinone ring has been the core structural skeleton in numerous alkaloids and a variety of natural products, such as schizocommunin,[9] luotonin A,[10] and oxoglyantrypine.[11] The range of biological activities and characteristic chemical structures has made synthetic studies of quinazolinones very attractive. On the other hand, the 4(3*H*)-pyrimidinone ring system also exhibits various biological activities; some of them have been used as kainate receptor antagonists,[12] mGluR5 antagonists,[13] AMPA receptors,[14] dipeptidyl peptidase IV (DPP-4) inhibitors,[15] and non-nucleoside HIV-1 reverse transcriptase inhibitors.[16] The introduction of a pyrimidinone ring to the quinazolinone system is expected to influence the biological activities significantly. However, there is no report about the synthesis of pyrimido[2,1-*b*]quinazoline-2,6-diones in the literature.

The Baylis–Hillman reaction provides a powerful method for the preparation of densely functionalized molecules via the construction of carbon–carbon bonds in a simple one-pot procedure.[17] These densely functionalized molecules usually known as Baylis–Hillman adducts have been employed recently in further preparation of various heterocyclic compounds, such as 1,4-oxazepan-7-ones,[18] chromenes,[19] benzoindazoles,[20] benzoxazonines,[21] and hexahydroisoindoles.[22] The aza-Wittig reactions of iminophosphoranes have also received great attention in view of their utility in the synthesis of heterocyclic compounds.[23] Thus, it is envisioned that combining the efficiency of the Baylis–Hillman reaction with a post-condensation aza-Wittig reaction would facilitate access to a series of biologically useful heterocycles.

Recently we have been interested in the synthesis of various heterocycles via aza-Wittig reaction[24] or by using the Baylis–Hillman adducts as starting materials.[25] Here we wish to report a one-pot synthesis of previously unreported 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-diones via a tandem aza-Wittig/nucleophilic addition/

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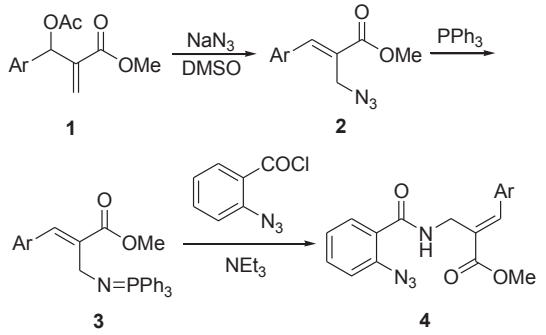
http://dx.doi.org/10.1016/j.tet.2014.12.006
0040-4020/

intramolecular cyclization/isomerization reaction, starting from the Baylis–Hillman adducts.

2. Results and discussion

Azides **2**, obtained easily from the reaction of Baylis–Hillman adducts **1** with sodium azide in DMSO,[26] reacted with triphenylphosphine to give iminophosphoranes **3** via Staudinger reaction. Further reactions of iminophosphorane **3** with 2-azidobenzoyl chloride in the presence of triethylamine produced the azides **4** in good overall yield (73–86%, Scheme 1 and Table 1).



Scheme 1. Preparation of the azides **4a**–**4d**.

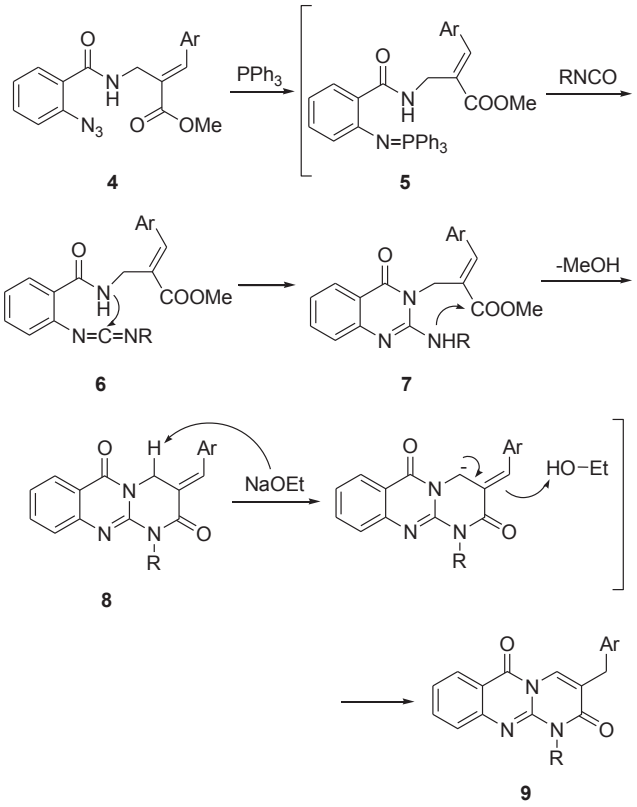
Table 1
Preparation of the azides **4a**–**4d**

Entry	Compd	Ar	Yield[a] (%)
1	**4a**	4-ClC_6H_4	86
2	**4b**	4-FC_6H_4	73
3	**4c**	4-$CF_3C_6H_4$	77
4	**4d**	Ph	82

[a] Isolated yields based on azides **2**.

When the azides **4** were treated with triphenylphosphine in toluene at room temperature for 4 h, iminophosphoranes **5** were formed. As iminophosphoranes **5** were reacted with isocyanate and subsequently treated with sodium ethoxide, the previously unreported 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-diones **9** were obtained directly in good overall yields (63–87%) (Scheme 2 and Table 2). Presumably, the conversion of **5** into **9** involves a consecutive process: an initial aza-Wittig reaction between the iminophosphorane **5** and the isocyanate gives a carbodiimide **6** as highly reactive intermediate, which easily undergoes ring closure through nucleophilic addition of the acylamino group to give quinazolinone **7**. Further cyclization of **7** in the presence of catalytic amount of sodium ethoxide produces **8**, which undertakes subsequent isomerization to give 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-dione **9** directly through 1,3-H shift under the basic condition. It is noteworthy that the reaction can be easily carried out at mild room temperature and the overall transformation is run in a simple one-pot procedure from azides **4**. Various isocyanates can be used in above one-pot cyclization to prepare 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-diones **9**. As aliphatic isocyanates (compounds **9e** and **9o**, R=alkyl) were used, moderate yields (63–69%) of the products were obtained, whereas when aromatic isocyanates (compounds **9a**–**d** and **9f**–**n**, R=aryl) were utilized, better yields (74–87%) were reached regardless of the substituents (Cl, F, CH_3, CF_3) on the benzene ring. The Ar group has no obvious effects on the reaction yields.

The structure of compounds **9** was confirmed by their spectrum data. For example, the ^{1}H NMR spectrum of **9a** shows one singlet and one doublets at 8.54 and 8.25 ppm due to the 4-H and 7-H of 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-dione ring. The signals



Scheme 2. Preparation of compounds **9a**–**9o**.

Table 2
Preparation of compounds **9a**–**9o**

Comp.	Ar	R	Yield[a] (%)
9a	4-ClC_6H_4	4-ClC_6H_4	87
9b	4-ClC_6H_4	4-$CH_3C_6H_4$	82
9c	4-FC_6H_4	4-ClC_6H_4	79
9d	4-ClC_6H_4	4-$CF_3C_6H_4$	81
9e	4-ClC_6H_4	*i*-Pr	69
9f	4-ClC_6H_4	4-FC_6H_4	83
9g	4-ClC_6H_4	3-$CH_3C_6H_4$	77
9h	4-$CF_3C_6H_4$	4-ClC_6H_4	81
9i	Ph	4-ClC_6H_4	77
9j	Ph	Ph	74
9k	Ph	4-$CH_3C_6H_4$	79
9l	4-FC_6H_4	Ph	86
9m	4-$CF_3C_6H_4$	4-$CH_3C_6H_4$	80
9n	4-$CF_3C_6H_4$	Ph	76
9o	4-ClC_6H_4	Et	63

[a] Isolated yields based on azides **4**.

attributable to other Ar–Hs are found at 7.68–7.20 ppm as multiplets. The signal of CH_2 is found at 3.84 ppm as singlet. The ^{13}C NMR spectrum data in **9a** showed the signals of two CON carbons at 160.6 and 158.2 ppm. The CH_2 carbon absorbs at 33.5 ppm. The MS spectrum of **9a** shows molecular ion peak at *m*/*z* 447 with 100% abundance.

3. Conclusion

We report herein a one-pot synthesis of 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-diones, by using a new tandem aza-Wittig/nucleophilic addition/intramolecular cyclization/isomerization reaction starting from the Baylis–Hillman adducts. Due to the very simple operation of the synthetic approach, this synthetic method

has the potential in preparation of various 1*H*-pyrimido[2,1-*b*] quinazoline-2,6-diones, which are of considerable interest as potential biological active compounds or pharmaceuticals.

4. Experimental

4.1. General

Melting points were determined using an X-4 model apparatus and were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. NMR was recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 600 or 400 spectrometer and resonances relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

4.2. Synthesis of azide 4

*4.2.1. Methyl 2-((2-azidobenzamido)methyl)-3-(4-chlorophenyl)acrylate (**4a**).* To the Baylis–Hillman azide **2a** (Ar=4-ClC_6H_4, 0.50 g, 2 mmol) in methylene dichloride (10 mL) was added dropwise triphenylphosphine (0.52 g, 2 mmol) in methylene dichloride (5 mL). After the mixture was stirred at room temperature for 2–4 h, triethylamine (0.30 g, 3 mmol) and 2-azidobenzoyl chloride (0.36 g, 2 mmol) were added sequentially and the resulted mixture was stirred for 4 h. After the solvent was evaporated under reduced pressure, the crude reaction mixture was purified by recrystallization from methylene dichloride/petroleum ether to give azide **4a** as white solid (0.64 g, 86%). Mp 67–69 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.12 (d, J=7.8 Hz, 1H, Ar–H), 8.01 (br, 1H, NH), 7.79 (s, 1H, =CH), 7.57–7.18 (m, 7H, Ar–H), 4.54 (d, J=5.4 Hz, 2H, NCH_2), 3.88 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.8, 164.1, 140.9, 136.9, 135.1, 132.3, 132.2, 131.9, 130.9, 128.9, 128.7, 128.3, 124.8, 118.2, 52.1, 36.9. Anal. Calcd for $C_{18}H_{15}ClN_4O_3$: C, 58.31; H, 4.08; N, 15.11. Found: C, 58.54; H, 4.21; N, 15.12.

*4.2.2. Methyl 2-((2-azidobenzamido)methyl)-3-(4-fluorophenyl)acrylate (**4b**).* Operation as above with the Baylis–Hillman azide **2b** (Ar=4-FC_6H_4, 0.47 g, 2 mmol), compound **4b** (0.52 g, 73%) was also isolated as white solid. Mp: 108–110 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.13 (d, J=7.8 Hz, 1H, Ar–H), 8.00 (br, 1H, NH), 7.81 (s, 1H, =CH), 7.64–7.12 (m, 7H, Ar–H), 4.55 (d, J=5.4 Hz, 2H, NCH_2), 3.88 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.6, 163.9, 161.9, 140.8, 136.7, 132.0, 131.9, 131.7, 131.5, 130.0, 127.4, 124.7, 124.6, 118.2, 118.1, 115.5, 115.3, 51.8, 36.7. Anal. Calcd for $C_{18}H_{15}FN_4O_3$: C, 61.01; H, 4.27; N, 15.81. Found: C, 61.13; H, 4.51; N, 15.52.

*4.2.3. Methyl 2-((2-azidobenzamido)methyl)-3-(4-(trifluoromethyl) phenyl)acrylate (**4c**).* Operation as above with the Baylis–Hillman azide **2c** (Ar=4-$CF_3C_6H_4$, 0.57 g, 2 mmol), compound **4c** (0.62 g, 77%) was also isolated as white solid. Mp: 171–172 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.13 (d, J=7.8 Hz, 1H, Ar–H), 8.06 (br, 1H, NH), 7.85 (s, 1H,=CH), 7.74–7.19 (m, 7H, Ar–H), 4.53 (d, J=5.4 Hz, 2H, NCH_2), 3.91 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.5, 164.1, 140.4, 140.3, 137.7, 136.9, 132.3, 132.2, 132.0, 131.9, 129.9, 129.7, 125.4, 125.1, 124.9, 124.7, 118.4, 118.2, 52.3, 36.9. Anal. Calcd for $C_{19}H_{15}F_3N_4O_3$: C, 56.44; H, 3.74; N, 13.86. Found: C, 56.72; H, 3.66; N, 13.74.

*4.2.4. Methyl 2-((2-azidobenzamido)methyl)-3-phenylacrylate (**4d**).* Operation as above with the Baylis–Hillman azide **2d** (Ar=Ph, 0.43 g, 2 mmol), compound **4d** (0.55 g, 82%) was also isolated as white solid. Mp: 132–133 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.87 (s, 1H, NH), 7.51–6.78 (m, 10H, Ar–H), 5.17 (s, 2H, NCH_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 169.8, 167.5, 142.1, 137.2, 134.6, 131.7, 131.5, 129.4, 128.8, 128.3, 127.8, 123.9, 118.1, 118.0, 51.9, 41.7. Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.24; H, 4.66; N, 16.54.

4.3. One-pot synthesis of 1*H*-pyrimido[2,1-*b*]quinazoline-2,6-diones 9

*4.3.1. 3-(4-Chlorobenzyl)-1-(4-chlorophenyl)-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9a**).* To the azide **4a** (Ar=4-ClC_6H_4, 0.37 g, 1 mmol) in toluene (5 mL), was added dropwise triphenylphosphine (0.26 g, 1 mmol) in toluene (5 mL). After the reaction mixture was stirred for 2–4 h at room temperature, 4-chlorophenylisocyanate (0.15 g, 1 mmol) was added. The reaction mixture was stirred for 1 h and then NaOEt (0.014 g, 0.2 mmol) in ethanol was added. The reaction mixture was stirred for further 1–2 h at room temperature. After the solvent was evaporated under reduced pressure, the crude reaction mixture was eluted with ether/petroleum ether (3:1) through a short silica gel column to give the compound **9a** as white solid (0.39 g, 87%), mp 288–289 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.54 (s, 1H, Ar–H), 8.25 (d, J=6.6 Hz, 1H, Ar–H), 7.68–7.20 (m, 11H, Ar–H), 3.84 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.6, 158.2, 147.2, 144.0, 135.8, 135.7, 134.8, 133.9, 132.9, 130.5, 130.1, 129.9, 129.7, 128.9, 127.5, 127.0, 125.5, 120.7, 116.3, 33.5; MS (EI, 70 eV) m/z (%) 447 (M^+, 100), 300 (11), 271 (29), 255 (9), 176 (14), 149 (16), 111 (22), 90 (18). Anal. Calcd for $C_{24}H_{15}Cl_2N_3O_2$: C, 64.30; H, 3.37; N, 9.37. Found: C, 64.13; H, 3.31; N, 9.62.

*4.3.2. 3-(4-Chlorobenzyl)-1-p-tolyl-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9b**).* Operation as above with the 4-methylphenylisocyanate (0.13 g, 1 mmol), compound **9b** (0.35 g, 82%) was also isolated as white solid. Mp: 287–288 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.54 (s, 1H, Ar–H), 8.24 (d, J=8.4 Hz, 1H, Ar–H), 7.67–7.13 (m, 11H, Ar–H), 3.85 (s, 2H, CH_2), 2.46 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.8, 158.3, 147.4, 144.3, 138.7, 135.8, 135.6, 132.8, 130.6, 130.2, 129.6, 129.5, 128.8, 128.2, 127.4, 127.0, 125.2, 120.8, 116.3, 33.5, 21.3; MS (EI, 70 eV) m/z (%) 427 (M^+, 100), 398 (6), 250 (14), 235 (8), 192 (4), 157 (11), 91 (8). Anal. Calcd for $C_{25}H_{18}ClN_3O_2$: C, 70.18; H, 4.24; N, 9.82. Found: C, 70.40; H, 4.43; N, 9.98.

*4.3.3. 3-(4-Fluorobenzyl)-1-(4-chlorophenyl)-1H-pyrimido[2,1-b] quinazoline-2,6-dione (**9c**).* Operation as above with the azide **4b** (Ar=4-FC_6H_4, 0.35 g, 1 mmol), compound **9c** (0.34 g, 79%) was also isolated as white solid. Mp: 278–279 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.52 (s, 1H, Ar–H), 8.25 (d, J=7.8 Hz, 1H, Ar–H), 7.69–7.01 (m, 11H, Ar–H), 3.85 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.7, 158.2, 147.2, 144.1, 135.8, 134.8, 134.0, 130.8, 130.7, 130.2, 130.1, 129.7, 127.5, 127.0, 125.5, 121.0, 116.4, 115.8, 115.6, 115.5, 33.3; MS (EI, 70 eV) m/z (%) 431 (M^+, 100), 402 (10), 291 (7), 270 (16), 192 (9), 133 (15), 111 (13), 90 (10). Anal. Calcd for $C_{24}H_{15}ClFN_3O_2$: C, 66.75; H, 3.50; N, 9.73. Found: C, 66.69; H, 3.70; N, 9.65.

*4.3.4. 3-(4-Chlorobenzyl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9d**).* Operation as above with the 4-trifluoromethylphenylisocyanate (0.19 g, 1 mmol), compound **9d** (0.39 g, 81%) was also isolated as white solid. Mp: 268–269 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.56 (s, 1H, Ar–H), 8.25 (d, J=7.8 Hz, 1H, Ar–H), 7.69–7.26 (m, 11H, Ar–H), 3.85 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.6, 158.2, 149.1, 147.1, 144.0, 135.8, 135.7, 133.7, 132.9, 130.5, 130.3, 129.9, 128.9, 127.5, 127.0, 125.6, 121.8, 120.6, 116.3, 33.5; MS (EI, 70 eV) m/z (%) 481 (M^+, 100), 422 (7), 321 (18), 305 (10), 193 (10), 176 (12), 149 (12), 125 (9), 90 (8). Anal. Calcd for $C_{25}H_{15}ClF_3N_3O_2$: C, 62.32; H, 3.14; N, 8.72. Found: C, 62.49; H, 3.10; N, 8.95.

*4.3.5. 3-(4-Chlorobenzyl)-1-isopropyl-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9e**).* Operation as above with the isopropylisocyanate (0.09 g, 1 mmol), compound **9e** (0.26 g, 69%) was

also isolated as white solid. Mp: 195–196 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.38 (s, 1H, Ar–H), 8.24 (d, J=8.4 Hz, 1H, Ar–H), 7.77–7.24 (m, 7H, Ar–H), 5.88–5.74 (m, 1H, NCH), 3.80 (s, 2H, CH_2), 1.62 (d, J=7.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.8, 158.6, 147.4, 136.0, 135.6, 132.7, 130.4, 129.1, 129.0, 128.9, 127.4, 126.6, 125.0, 120.8, 116.0, 47.9, 33.4, 19.2; MS (EI, 70 eV) m/z (%) 379 (M^+, 100), 308 (20), 274 (13), 198 (21), 176 (12), 145 (18), 136 (9), 119 (6). Anal. Calcd for $C_{21}H_{18}ClN_3O_2$: C, 66.40; H, 4.78; N, 11.06. Found: C, 66.54; H, 4.70; N, 11.25.

*4.3.6. 3-(4-Chlorobenzyl)-1-(4-fluorophenyl)-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9f**).* Operation as above with the 4-fluorophenylisocyanate (0.14 g, 1 mmol), compound **9f** (0.36 g, 83%) was also isolated as white solid. Mp: 266–267 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.55 (s, 1H, Ar–H), 8.25 (d, J=7.8 Hz, 1H, Ar–H), 7.68–7.24 (m, 11H, Ar–H), 3.85 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.8, 158.2, 147.2, 135.8, 135.7, 132.9, 131.2, 130.5, 130.4, 130.3, 129.8, 128.9, 127.5, 127.0, 125.5, 120.7, 116.6, 116.4, 116.3, 33.5; MS (EI, 70 eV) m/z (%) 431 (M^+, 100), 402 (6), 272 (7), 254 (27), 239 (20), 184 (11), 160 (12), 125 (5), 95 (17). Anal. Calcd for $C_{24}H_{15}ClFN_3O_2$: C, 66.75; H, 3.50; N, 9.73. Found: C, 66.69; H, 3.71; N, 9.55.

*4.3.7. 3-(4-Chlorobenzyl)-1-(m-tolyl)-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9g**).* Operation as above with the 3-methylphenylisocyanate (0.13 g, 1 mmol), compound **9g** (0.33 g, 77%) was also isolated as white solid. Mp: 256–257 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.53 (s, 1H, Ar–H), 8.22 (d, J=7.2 Hz, 1H, Ar–H), 7.65–7.06 (m, 11H, Ar–H), 3.83 (s, 2H, CH_2), 2.42 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.8, 158.3, 147.3, 144.2, 139.4, 135.8, 135.6, 135.4, 132.7, 130.5, 129.7, 129.2, 128.9, 128.8, 127.3, 127.0, 125.4, 125.2, 120.7, 116.2, 33.4, 21.4; MS (EI, 70 eV) m/z (%) 427 (M^+, 100), 398 (8), 250 (14), 235 (8), 192 (5), 158 (11), 149 (6), 91 (17), 90 (7). Anal. Calcd for $C_{25}H_{18}ClN_3O_2$: C, 70.18; H, 4.24; N, 9.82. Found: C, 70.39; H, 4.50; N, 9.55.

*4.3.8. 1-(4-Chlorophenyl)-3-(4-(trifluoromethyl)benzyl)-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9h**).* Operation as above with the azide **4c** (Ar=4-$F_3CC_6H_4$, 0.40 g, 1 mmol), compound **9h** (0.39 g, 81%) was also isolated as white solid. Mp: 288–290 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.61 (s, 1H, Ar–H), 8.25 (d, J=8.4 Hz, 1H, Ar–H), 7.70–7.20 (m, 11H, Ar–H), 3.94 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.6, 158.2, 147.2, 144.0, 141.4, 135.9, 135.8, 134.8, 133.9, 130.2, 130.1, 130.0, 129.5, 127.5, 127.0, 125.8, 125.7, 125.6, 120.1, 116.4, 34.0; MS (EI, 70 eV) m/z (%) 481 (M^+, 100), 452 (5), 271 (10), 255 (4), 192 (7), 167 (9), 111 (8), 90 (7). Anal. Calcd for $C_{25}H_{15}ClF_3N_3O_2$: C, 62.32; H, 3.14; N, 8.72. Found: C, 62.49; H, 3.30; N, 8.61.

*4.3.9. 3-Benzyl-1-(4-chlorophenyl)-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9i**).* Operation as above with the azide **4d** (Ar=Ph, 0.34 g, 1 mmol), compound **9i** (0.32 g, 77%) was also isolated as white solid. Mp: >300 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.51 (s, 1H, Ar–H), 8.23 (d, J=7.8 Hz, 1H, Ar–H), 7.68–7.21 (m, 12H, Ar–H), 3.88 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.7, 158.2, 147.2, 144.1, 137.1, 135.7, 134.7, 134.0, 130.1, 129.8, 129.7, 129.2, 128.8, 127.4, 127.0, 126.9, 125.4, 121.2, 116.4, 33.9; MS (EI, 70 eV) m/z (%) 413 (M^+, 100), 384 (5), 271 (16), 220 (6), 192 (7), 167 (9), 142 (23). Anal. Calcd for $C_{24}H_{16}ClN_3O_2$: C, 69.65; H, 3.90; N, 10.15. Found: C, 69.69; H, 3.72; N, 10.25.

*4.3.10. 3-Benzyl-1-phenyl-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9j**).* Operation as above with the azide **4d** (Ar=Ph, 0.34 g, 1 mmol) and phenylisocyanate (0.12 g, 1 mmol), compound **9j** (0.28 g, 74%) was also isolated as white solid. Mp: >300 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.52 (s, 1H, Ar–H), 8.23 (d, J=7.2 Hz, 1H, Ar–H), 7.64–7.26 (m, 13H, Ar–H), 3.89 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.9, 158.3, 147.3, 144.3, 137.3, 135.6, 129.7, 129.4, 129.2, 128.9, 128.8, 128.6, 127.4, 127.2, 127.1, 127.0, 125.2, 121.3, 116.3, 34.0; MS (EI, 70 eV) m/z (%) 379 (M^+, 100), 350 (4), 236 (19), 142 (11), 115 (13), 77 (25). Anal. Calcd for $C_{24}H_{17}N_3O_2$: C, 75.97; H, 4.52; N, 11.08. Found: C, 75.69; H, 4.61; N, 11.25.

*4.3.11. 3-Benzyl-1-(p-tolyl)-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9k**).* Operation as above with the azide **4d** (Ar=Ph, 0.34 g, 1 mmol) and 4-methylphenylisocyanate (0.13 g, 1 mmol), compound **9k** (0.31 g, 79%) was also isolated as white solid. Mp: >300 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.50 (s, 1H, Ar–H), 8.22 (d, J=7.2 Hz, 1H, Ar–H), 7.64–7.15 (m, 12H, Ar–H), 3.88 (s, 2H, CH_2), 2.46 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 161.0, 158.3, 147.4, 147.3, 144.3, 138.7, 137.3, 135.5, 133.0, 130.1, 129.6, 128.8, 128.2, 127.4, 127.0, 126.9, 125.1, 121.4, 116.3, 34.0, 21.3; MS (EI, 70 eV) m/z (%) 393 (M^+, 100), 364 (2), 288 (4), 235 (10), 142 (5), 91 (8). Anal. Calcd for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 76.25; H, 4.60; N, 10.55.

*4.3.12. 3-(4-Fluorobenzyl)-1-phenyl-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9l**).* Operation as above with the azide **4b** (Ar=4-FC_6H_4, 0.35 g, 1 mmol) and phenylisocyanate (0.12 g, 1 mmol), compound **9l** (0.34 g, 86%) was also isolated as white solid. Mp: >300 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.54 (s, 1H, Ar–H), 8.24 (d, J=7.8 Hz, 1H, Ar–H), 7.67–7.01 (m, 12H, Ar–H), 3.86 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 163.1, 160.8, 158.3, 147.4, 144.3, 135.6, 133.0, 130.8, 130.7, 129.7, 129.5, 128.8, 128.6, 127.4, 127.0, 125.3, 121.1, 116.3, 115.7, 115.5, 33.3; MS (EI, 70 eV) m/z (%) 397 (M^+, 100), 368 (5), 221 (12), 161 (5), 133 (16), 90 (5). Anal. Calcd for $C_{24}H_{16}FN_3O_2$: C, 72.54; H, 4.06; N, 10.57. Found: C, 72.55; H, 4.20; N, 10.35.

*4.3.13. 3-(4-(Trifluoromethyl)benzyl)-1-(p-tolyl)-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9m**).* Operation as above with the azide **4c** (Ar=4-$F_3CC_6H_4$, 0.40 g, 1 mmol) and 4-methylphenylisocyanate (0.13 g, 1 mmol), compound **9m** (0.37 g, 80%) was also isolated as white solid. Mp: 295–296 °C; ^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm) 8.77 (s, 1H, Ar–H), 8.15 (d, J=7.8 Hz, 1H, Ar–H), 7.74–7.18 (m, 11H, Ar–H), 3.98 (s, 2H, CH_2), 2.40 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.8, 158.4, 147.4, 144.3, 141.6, 138.8, 135.7, 132.8, 130.3, 130.2, 129.9, 129.8, 129.5, 128.3, 128.2, 127.4, 127.1, 125.7, 125.3, 120.3, 116.3, 34.0, 21.3; MS (EI, 70 eV) m/z (%) 461 (M^+, 100), 432 (3), 367 (4), 317 (17), 288 (5), 221 (5), 191 (5). Anal. Calcd for $C_{26}H_{18}F_3N_3O_2$: C, 67.68; H, 3.93; N, 9.11. Found: C, 67.45; H, 3.80; N, 9.15.

*4.3.14. 1-Phenyl-3-(4-(trifluoromethyl)benzyl)-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9n**).* Operation as above with the azide **4c** (Ar=4-$F_3CC_6H_4$, 0.40 g, 1 mmol) and phenylisocyanate (0.12 g, 1 mmol), compound **9n** (0.34 g, 76%) was also isolated as white solid. Mp: >300 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.62 (s, 1H, Ar–H), 8.25 (d, J=8.4 Hz, 1H, Ar–H), 7.66–7.26 (m, 12H, Ar–H), 3.95 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.7, 158.3, 147.3, 144.2, 141.5, 135.7, 135.5, 130.0, 129.5, 129.4, 129.1, 128.9, 128.5, 127.4, 127.0, 125.7, 125.6, 125.4, 125.3, 120.2, 116.3, 34.0; MS (EI, 70 eV) m/z (%) 446 (M^+–1, 100), 418 (7), 338 (22), 221 (16), 150 (8), 90 (9), 77 (18). Anal. Calcd for $C_{25}H_{16}F_3N_3O_2$: C, 67.11; H, 3.60; N, 9.39. Found: C, 67.25; H, 3.50; N, 9.55.

*4.3.15. 3-(4-Chlorobenzyl)-1-ethyl-1H-pyrimido[2,1-b]quinazoline-2,6-dione (**9o**).* Operation as above with ethylisocyanate (0.07 g, 1 mmol), compound **9o** (0.23 g, 63%) was also isolated as white solid. Mp: >300 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.39 (s, 1H, Ar–H), 8.20 (d, J=8.0 Hz, 1H, Ar–H), 7.74–7.24 (m, 7H, Ar–H), 4.40 (q, J=7.2 Hz, 2H, NCH_2), 3.80 (s, 2H, CH_2), 1.33 (t, J=7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.1, 158.4, 147.7, 142.9, 135.9, 135.6, 132.7, 130.4, 129.0, 128.8, 127.4, 126.6, 124.9, 120.3, 116.1, 37.9, 33.4, 12.4; MS (EI, 70 eV) m/z (%) 365 (M^+, 100), 337 (90), 274 (25),

198 (70), 145 (31), 90 (17). Anal. Calcd for $C_{20}H_{16}ClN_3O_2$: C, 65.67; H, 4.41; N, 11.49. Found: C, 65.84; H, 4.50; N, 11.27.

Acknowledgements

We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (No. 21172085, 21032001).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.12.006.

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