

# Synthesis of novel 5-phenylimidazo[1,2-*c*]quinazolin-3-amine derivatives via Groebke–Blackburn–Bienaymé multicomponent reaction

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**Abstract** We have developed an efficient and environmentally benign one-pot procedure for synthesis of novel *N*-alkyl-2-aryl-5-phenylimidazo[1,2-*c*]quinazolin-3-amine derivatives by use of the Groebke–Blackburn–Bienaymé multicomponent reaction. The title compounds were synthesized in good yields from 2-phenylquinazolin-4-amine, aromatic aldehydes, and isocyanides in the presence of ammonium chloride under solvent-free conditions.

**Keywords** Groebke–Blackburn–Bienaymé · Isocyanides · Multicomponent reactions · Phenylimidazo[1,2-*c*]quinazolines

## Introduction

Fused imidazo[1,2-*c*]quinazoline heterocycles are of interest to medicinal chemists because of their wide variety of pharmacological and biological properties. In this regard, versatile strategies for obtaining new structures are of great interest to synthetic chemists [1]. Some imidazo[1,2-*c*]quinazolines synthesized by Bourguignon et al. [2] act as coronary smooth muscle relaxants, and Hansen

et al. [3] have reported they are also useful for preparation of psychopharmaceuticals, for example anticonvulsants, anxiolytics, hypnotics, antipsychotics, and antiemetics, for improving cognitive function of the brains of mammals, or as benzodiazepine antagonists. Imidazo[1,2-*c*]quinazolines synthesized by Chern et al. [4] were useful as active ingredients for treatment of hypertension. Their antioxidant activity acts as a potent inhibitor of lipid peroxidation [5]. Literature survey shows that 6-arylbenzimidazo[1,2-*c*]quinazolines act as inhibitors of LPS-induced TNF- $\alpha$  secretion [6]. Therefore, new synthetic methods for synthesis of imidazo[1,2-*c*]quinazolines need active study.

In recent years there has been much interest in the use of solvent-free conditions. Because there is no reaction medium to collect, purify, and recycle, they result in reduced pollution, low cost, and simplicity in process and handling, which are very important in industry [7]. Sequential solvent-free reactions are possible in high-yielding systems [8]. In recent years, solvent-free conditions for synthesis of heterocyclic compounds have become increasingly significant and are regarded as important and useful synthetic methods [9].

To the best of our knowledge, there is no report of the synthesis of *N*-alkyl-2-aryl-5-phenylimidazo[1,2-*c*]quinazolines. Herein, in the context of our interest in designing new heterocyclic structures [10–12], we wish to report a green procedure for synthesis of novel imidazo[1,2-*c*]quinazolines **6** by use of the Groebke–Blackburn–Bienaymé multicomponent reaction under solvent-free conditions (Scheme 1).

## Results and discussion

We have developed a method for synthesis of novel imidazo[1,2-*c*]quinazolines **6** based on the Groebke–

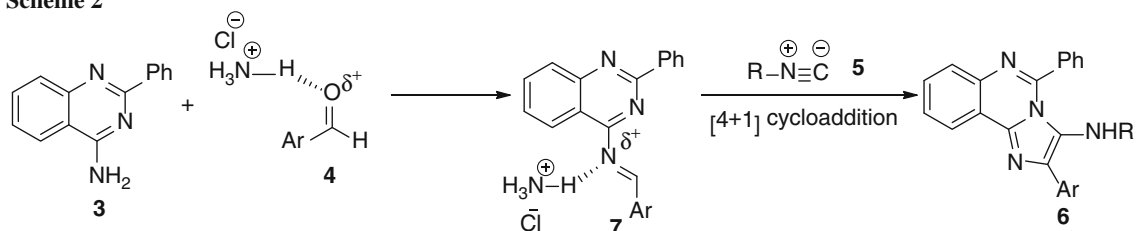
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Scheme 2



different aromatic aldehydes and isocyanides were reacted with 2-phenylquinazolin-4-amine **3** in the presence of ammonium chloride; the corresponding compounds **6** were obtained in good yields (Table 2). The results showed that the reaction is compatible with different benzaldehydes including those with electron-donating and electron-withdrawing substituents at different positions.

The sequence of reactions used for preparation of imidazo[1,2-*c*]quinazolines **6** is depicted in Scheme 2. The reaction begins by formation of iminium ion **7** by condensation of the 2-phenylquinazolin-4-amine **3** and aromatic aldehydes **4**, probably catalyzed by  $\text{NH}_4\text{Cl}$ . Nonconcerted [4 + 1] cycloaddition between **7** and isocyanide **5** then leads to formation of the product **6** [13–15].

## Conclusion

We report a convenient, green method for preparation of *N*-alkyl-2-aryl-5-phenylimidazo[1,2-*c*]quinazolin-3-amine derivatives by three-component reaction of 2-phenylquinazolin-4-amine, aromatic aldehydes, and isocyanides in the presence of ammonium chloride under solvent-free conditions. The main advantages of the procedure include preparation of new compounds in the absence of expensive catalyst and solvent, good yields, and product diversity. It is worth mentioning that better yields of products and shorter reaction times were obtained under solvent-free conditions than when a variety of different solvents were used. Use of solvent-free conditions is vital for environmental reasons, among other advantages.

## Experimental

All chemicals were purchased from Merck and Sigma-Aldrich and used without further purification. Melting points were taken on a Kofler hot-stage apparatus.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker FT-500, with TMS as internal standard. IR spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer in KBr. Mass spectra were determined on an Agilent Technology (HP)

mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed with an Elementar Analysensystem VarioEL in CHNS mode.

### General procedure for synthesis of 5-phenylimidazo[1,2-*c*]quinazolin-3-amine derivatives **6**

A mixture of 0.26 g 2-phenylquinazolin-4-amine **3** (1 mmol), aromatic aldehyde **4** (1 mmol), isocyanide **5** (1.2 mmol), and ammonium chloride (1 mmol) was stirred at 150 °C for 2–3 h. After completion of the reaction (checked by TLC) the mixture was cooled to room temperature and the residue was purified by column chromatography using silicagel and petroleum ether–ethyl acetate (5:1) as eluent.

#### *N*-tert-Butyl-2-(2-fluorophenyl)-5-phenylimidazo[1,2-*c*]quinazolin-3-amine (**6a**, $\text{C}_{26}\text{H}_{23}\text{FN}_4$ )

Yellow crystals; m.p.: 164–166 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.66 (d,  $J$  = 6.8 Hz, 1H,  $\text{H}_7$ ), 8.00 (d,  $J$  = 7.4 Hz, 2H,  $\text{H}_{10}$ ,  $\text{H}_6'$ ), 7.81–7.79 (m, 2H,  $\text{H}_8$ ,  $\text{H}_9$ ), 7.70–7.53 (m, 5H, Ph), 7.37–7.30 (m, 2H,  $\text{H}_{3'}$ ,  $\text{H}_{5'}$ ), 7.18 (t,  $J$  = 6.8 Hz, 1H,  $\text{H}_{4'}$ ), 2.75 (d,  $J$  = 6.0 Hz, 1H, NH), 0.60 (s, 9H, *tert*-butyl) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 159.3 (d,  $J_{\text{C-F}}$  = 244.1 Hz), 147.2, 141.3, 140.3, 134.4, 133.9, 131.5, 129.5, 129.4, 129.3, 129.2, 127.8, 127.6, 127.5, 127.0, 124.2, 122.2 (d,  $J_{\text{C-F}}$  = 31.0 Hz), 121.8, 118.0, 115.2 (d,  $J_{\text{C-F}}$  = 22.7 Hz), 55.2, 28.5 ppm; IR (KBr):  $\bar{\nu}$  = 3,394, 3,237, 2,968, 2,863, 1,614, 1,595, 1,553  $\text{cm}^{-1}$ ; MS (70 eV):  $m/z$  = 410.19 ( $\text{M}^+$ ).

#### 2-(4-Chlorophenyl)-*N*-cyclohexyl-5-phenylimidazo[1,2-*c*]quinazolin-3-amine (**6b**, $\text{C}_{28}\text{H}_{25}\text{ClN}_4$ )

Yellow crystals; m.p.: 259–261 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.66 (d,  $J$  = 7.6 Hz, 1H,  $\text{H}_7$ ), 8.28 (d,  $J$  = 8.5 Hz, 2H,  $\text{H}_{2'}$ ,  $\text{H}_6'$ ), 7.97 (d,  $J$  = 8.3 Hz, 1H,  $\text{H}_{10}$ ), 7.77–7.76 (m, 2H,  $\text{H}_8$ ,  $\text{H}_9$ ), 7.70–7.63 (m, 5H, Ph), 7.41 (d,  $J$  = 8.5 Hz, 2H,  $\text{H}_{3'}$ ,  $\text{H}_{5'}$ ), 2.42 (s, 1H, NH), 2.30–2.26 (m, 1H, NCH), 1.39–0.62 (m, 10H, cyclohexyl) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 145.1, 141.2, 140.3, 134.9, 130.6, 130.1, 129.5, 129.3, 129.2, 128.6, 128.5, 128.3, 128.2, 127.8, 127.5, 125.4, 125.3, 122.0, 56.3, 31.9, 29.0, 28.2 ppm; IR (KBr):  $\bar{\nu}$  = 3,415, 3,231, 3,131, 2,924,

1,614, 1,565  $\text{cm}^{-1}$ ; MS (70 eV):  $m/z = 454.17$  ( $\text{M}^+ + 2$ ), 452.18 ( $\text{M}^+$ ).

*N*-Cyclohexyl-5-phenyl-2-(pyridine-4-yl)imidazo[1,2-*c*]-quinazolin-3-amine (**6c**,  $\text{C}_{27}\text{H}_{25}\text{N}_5$ )

Yellow crystals; m.p.: 204–206 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.68$ – $8.63$  (m, 3H,  $\text{H}_{3'}$ ,  $\text{H}_{5'}$ ,  $\text{H}_7$ ), 8.28–8.25 (m, 2H,  $\text{H}_{2'}$ ,  $\text{H}_{6'}$ ), 7.96 (d,  $J = 7.6$  Hz, 1H,  $\text{H}_{10}$ ), 7.77–7.74 (m, 2H,  $\text{H}_8$ ,  $\text{H}_9$ ), 7.70–7.65 (m, 5H, Ph), 2.53 (d,  $J = 4.1$  Hz, 1H, NH), 2.35–2.30 (m, 1H, NCH), 1.44–0.61 (m, 10H, cyclohexyl) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 148.5$ , 145.7, 141.9, 141.0, 140.2, 134.0, 131.9, 130.3, 129.7, 128.8, 128.5, 128.0, 127.9, 127.6, 121.9, 121.1, 118.3, 57.6, 32.2, 24.9, 24.1 ppm; IR (KBr):  $\bar{\nu} = 3,379$ , 3,128, 2,928, 2,852, 1,712, 1,598, 1,572  $\text{cm}^{-1}$ ; MS (70 eV):  $m/z = 419.21$ .

*N*-Cyclohexyl-2-(4-nitrophenyl)-5-phenylimidazo[1,2-*c*]-quinazolin-3-amine (**6d**,  $\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2$ )

Yellow crystals; m.p.: 260–261 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.66$  (dd,  $J = 8.3$ , 1.7 Hz, 1H,  $\text{H}_7$ ), 8.54 (d,  $J = 9.0$  Hz, 2H,  $\text{H}_{3'}$ ,  $\text{H}_{5'}$ ), 8.29 (d,  $J = 9.0$  Hz, 2H,  $\text{H}_{2'}$ ,  $\text{H}_{6'}$ ), 7.98 (dd,  $J = 8.3$ , 1.4 Hz, 1H,  $\text{H}_{10}$ ), 7.78–7.76 (m, 2H,  $\text{H}_8$ ,  $\text{H}_9$ ), 7.73–7.66 (m, 5H, Ph), 2.53 (d,  $J = 5.1$  Hz, 1H, NH), 2.34–2.33 (m, 1H, NCH), 1.60–0.88 (m, 10 H, cyclohexyl) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 145.9$ , 145.6, 141.0, 140.3, 140.2, 134.0, 130.4, 130.3, 129.8, 128.6, 128.3, 128.1, 127.9, 127.7, 127.3, 123.1, 122.0, 118.2, 57.6, 32.2, 24.9, 24.1 ppm; IR (KBr):  $\bar{\nu} = 3,376$ , 3,119, 2,926, 2,853, 1,596, 1,569, 1,336  $\text{cm}^{-1}$ ; MS (70 eV):  $m/z = 463.20$ .

*N*-tert-Butyl-2-(4-fluorophenyl)-5-phenylimidazo[1,2-*c*]-quinazolin-3-amine (**6e**,  $\text{C}_{26}\text{H}_{23}\text{FN}_4$ )

Yellow crystals; m.p.: 165–167 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 8.49$  (d,  $J = 6.6$  Hz, 1H,  $\text{H}_7$ ), 7.95–7.71 (m, 6H, ArH), 7.58–7.33 (m, 6H, ArH), 3.12 (bs, 1H, NH), 0.34 (s, 9H, *tert*-butyl) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 159.5$  (d,  $J_{\text{C-F}} = 245.5$  Hz), 147.4, 140.3 (d,  $J_{\text{C-F}} = 45.0$  Hz), 134.5, 132.3, 130.0, 129.7, 128.4, 128.2 (d,  $J_{\text{C-F}} = 23.5$  Hz), 127.9, 127.5, 127.3, 124.7, 124.5, 122.7 (d,  $J_{\text{C-F}} = 13.4$  Hz), 121.8, 118.1, 115.6 (d,  $J_{\text{C-F}} = 21.5$  Hz), 54.8, 28.7 ppm; IR (KBr):  $\bar{\nu} = 3,421$ , 2,975, 1,654, 1,597, 1,557, 1,488  $\text{cm}^{-1}$ ; MS (70 eV):  $m/z = 410.19$ .

*N*-tert-Butyl-2-(4-nitrophenyl)-5-phenylimidazo[1,2-*c*]-quinazolin-3-amine (**6f**,  $\text{C}_{26}\text{H}_{23}\text{N}_5\text{O}_2$ )

Yellow crystals; m.p.: 264–265 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.67$  (d,  $J = 6.3$  Hz, 1H,  $\text{H}_7$ ), 8.54 (d,  $J = 7.4$  Hz, 2H,  $\text{H}_{3'}$ ,  $\text{H}_{5'}$ ), 8.27 (d,  $J = 7.4$  Hz, 2H,  $\text{H}_{2'}$ ,  $\text{H}_{6'}$ ), 7.98 (d,  $J = 7.4$  Hz, 1H,  $\text{H}_{10}$ ), 7.78–7.76 (m, 2H,  $\text{H}_8$ ,  $\text{H}_9$ ), 7.72–7.66 (m, 5H, Ph), 2.52 (s, 1H, NH), 0.53 (s, 9H, *tert*-butyl) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 146.2$ , 146.1, 141.9, 141.0, 140.6, 136.0, 134.7, 130.3, 129.9,

128.7, 128.4, 128.1, 128.0, 127.6, 127.1, 122.9, 122.0, 118.0, 56.8, 28.9 ppm; IR (KBr):  $\bar{\nu} = 3,390$ , 2,967, 1,599, 1,516, 1,466, 1,336  $\text{cm}^{-1}$ ; MS (70 eV):  $m/z = 437.19$  ( $\text{M}^+$ ).

*N*-tert-Butyl-2-(4-methoxyphenyl)-5-phenylimidazo[1,2-*c*]-quinazolin-3-amine (**6g**,  $\text{C}_{27}\text{H}_{26}\text{N}_4\text{O}$ )

Yellow crystals; m.p.: 163–165 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.71$  (d,  $J = 8.0$  Hz, 1H,  $\text{H}_7$ ), 8.18–7.95 (m, 3H,  $\text{H}_8$ ,  $\text{H}_9$ ,  $\text{H}_{10}$ ), 7.78 (d,  $J = 7.0$ , 2H,  $\text{H}_{2'}$ ,  $\text{H}_{6'}$ ), 7.68–7.61 (m, 5H, Ph), 6.95 (d,  $J = 7.0$  Hz, 2H,  $\text{H}_{3'}$ ,  $\text{H}_{5'}$ ), 3.84 (s, 3H,  $\text{OCH}_3$ ), 2.41 (s, 1H, NH), 0.53 (s, 9H, *tert*-butyl) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 158.7$ , 146.4, 143.6, 143.5, 141.1, 141.0, 140.5, 135.0, 129.9, 129.3, 128.4, 128.3, 127.6, 127.4, 126.7, 124.6, 122.0, 113.0, 55.9, 54.7, 28.9 ppm; IR (KBr):  $\bar{\nu} = 3,380$ , 2,960, 2,837, 1,613, 1,567, 1,506  $\text{cm}^{-1}$ ; MS (70 eV):  $m/z = 422.21$  ( $\text{M}^+$ ).

*N*-tert-Butyl-5-phenyl-2-(3,4,5-trimethoxyphenyl)-imidazo[1,2-*c*]quinazolin-3-amine (**6h**,  $\text{C}_{29}\text{H}_{30}\text{N}_4\text{O}_3$ )

Yellow crystals; m.p.: 208–210 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.74$  (d,  $J = 7.5$  Hz, 1H,  $\text{H}_7$ ), 7.97 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_{10}$ ), 7.80–7.78 (m, 2H,  $\text{H}_8$ ,  $\text{H}_9$ ), 7.67–7.60 (m, 7H, ArH), 3.99 (s, 6H,  $\text{OCH}_3$ ), 3.91 (s, 3H,  $\text{OCH}_3$ ), 2.42 (s, 1H, NH), 0.59 (s, 9H, *tert*-butyl) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 152.9$ , 152.0, 146.6, 141.4, 141.1, 139.2, 137.9, 135.4, 130.5, 130.1, 129.0, 128.7, 128.3, 128.0, 127.2, 125.5, 122.7, 105.9, 61.0, 56.6, 56.3, 29.4 ppm; IR (KBr):  $\bar{\nu} = 3,357$ , 2,964, 1,605, 1,589, 1,500, 1,460  $\text{cm}^{-1}$ ; MS (70 eV):  $m/z = 482.23$  ( $\text{M}^+$ ).

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## References

- Cardellini M, Franchetti P, Grifantini M, Martelli S, Petrelli F (1975) *Farmacologia* 30:536
- Bourguignon JJ, Wermuth CG, Renaud de la Faverie JF, Thollon C, Lombet A (1992) Preparation of imidazo[1,2-*c*]quinazolinones as smooth muscle relaxants. US Patent 5,128,338, Jul 7, 1992. *Chem Abstr* 116:21068
- Hansen HC, Kristiansen M (1995) Imidazoquinazoline compounds and their use. US Patent 5,371,080, Dec 6, 1994. *Chem Abstr* 122:105917
- Chern JW, Lu GY, Lai YJ, Yen MH, Tao PL (1996) 3-Substituted methyl-2,3-dihydroimidazo[1,2-*c*]quinazoline derivatives, their preparation, and their use for treatment of hypertension and dysuria. US Patent 5,512,677, Apr 30, 1996; (1994). *Chem Abstr* 121:222010
- Domány G, Gizur T, Gere A, Takács-Novák K, Farsang G, Ferenczy GG, Tárkányi G, Demeter M (1998) *Eur J Med Chem* 33:181
- Galarce GD, Foncea RE, Edwards AM, Pessoa-Mahana H, Pessoa-Mahana CD, Ebensperger RA (2008) *Biol Res* 41:43
- Tanaka K, Toda F (2000) *Chem Rev* 100:1025
- Cave GWV, Raston CL, Scott JL (2001) *Chem Commun* 21:2159

9. Martins MAP, Frizzo CP, Moreira DN, Buriol L, Machado P (2009) *Chem Rev* 109:4140
10. Mahdavi M, Asadi M, Saeedi M, Ebrahimi M, Rasouli MA, Ranjbar PR, Foroumadi A, Shafiee A (2012) *Synthesis* 44:3649
11. Mahdavi M, Asadi M, Saeedi M, Rezaei Z, Moghbel H, Foroumadi A, Shafiee A (2012) *Synlett* 23:2521
12. Khoobi M, Alipour M, Zarei S, Jafarpour F, Shafiee A (2012) *Chem Commun* 48:2985
13. Groebke K, Weber L, Mehlin F (1998) *Synlett* 661
14. Blackburn C, Guan B, Fleming P, Shiosaki K, Tsai S (1998) *Tetrahedron Lett* 39:3635
15. Bienaymé H, Bouzid K (1998) *Angew Chem Int Ed* 37:2234
16. Sharma A, Li H (2011) *Synlett* 1407
17. Rousseau AL, Matlaba P, Parkinson CJ (2007) *Tetrahedron Lett* 48:4079
18. Adib M, Mahdavi M, Noghani MA, Mirzaei P (2007) *Tetrahedron Lett* 48:7263
19. Rostamnia S, Lamei K, Mohammadquli M, Sheykhan M, Heydari A (2012) *Tetrahedron Lett* 53:5257
20. Maiti B, Chanda K, Selvaraju M, Tseng CC, Sun CM (2013) *ACS Comb Sci* 15:291
21. Smyrl NR, Smithwick RW (1982) *J Heterocycl Chem* 19:493
22. Shaabani A, Rezazadeh F, Soleimani E (2008) *Monatsh Chem* 139:931
23. Bonne D, Dekhane M, Zhu J (2004) *Org Lett* 6:4771
24. Bonne D, Dekhane M, Zhu J (2005) *Org Lett* 7:5285