Photosynthesis of novel 4-arylamino-2-phenyl-6-substituted-quinazoline

Zhi-Yong Xing, Ying Fu and Fei Ye*

Department of Applied Chemistry, College of Science, Northeast Agricultural University, Harbin 150030, P.R. China
E-mail: yefei@neau.edu.cn

DOI: http://dx.doi.org/10.3998/ark.5550190.0013.924

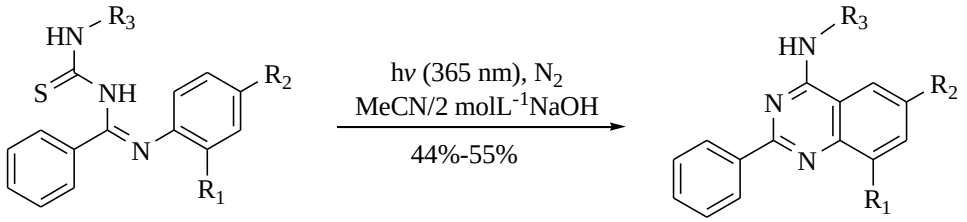
Abstract
A new and efficient strategy, the synthesis of novel quinazoline derivatives via the cyclization of *N*,*N*'–disubstituted thiourea derivatives in the solvent of acetontrile and aqueous NaOH under ultraviolet light irradiation, has been developed. All of these compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, Elemental analysis and Mass spectrometry.

Keywords: Photosynthesis, quinazoline, cyclization, thiourea, irradiation

Introduction

Quinazoline derivatives have attracted a great deal of interest, mainly concern for their synthesis, reactions and biological properties, as this structure appeared in a large number of pharmaceutical agents and natural products.[1] These compounds were endowed with a large spectrum of biological activities, including remarkable antiinflammatory,[2] antifungicidal,[3] antibacterial,[4] antihypertensive,[5] α_1-adrenoceptor antagonists,[6] antiplasmodial[7] and inhibitors of the epidermal growth factor receptor (EGFR).[8] In this rapidly developing field, many synthetic approaches have been reported using conventional solution phase synthesis with different starting materials, such as 4-chloro-quinazoline,[9] 2-nitrobenzoic acid,[10] anthranilic acid,[11] 2-aminobenzonitrile[12] and anthranilamide.[13] Since solution phase synthesis usually required tedious workup after each reaction step, several research groups developed new methods for the synthesis of quinazolines in recent years, such as solid-phase,[14] microwaves,[15] cyclization,[16] oxidation,[17] one-pot synthesis[18] and electrocyclization.[19] Most of these new methods afforded good yield and short-time consuming, but the materials used for the synthesis was either unavailable or requireing muti-step preparation. Although quninazoline derivatives have been synthesized successfully, photochemical method utilized for the synthesis of quinazoline derivatives has scarcely been reported. [20] In continues our effort for the synthesis of heterocycle

compounds, we hereby reported the synthesis of novel quianzoline derivatives via the cyclization of *N*,*N*'–disubstituted thiourea derivatives (**1a-f**) under ultraviolet light irradiation (Scheme 1).



1a-f **2a-f**

Scheme 1

Results and Discussion

The *N*,*N*'–disubstituted thiourea derivatives **1a-f** were prepared as described in the literature.[21] The photocyclization of thiourea derivative **1a** with a high-pressure mercury lamp (365 nm) in acetonitrile under N_2 protection at room temperature was chosen as a model reaction. Initially, the photochemical experiment in the presence of organic base (triethylamine) and inorganic base (sodium hydroxide) were explored.[20] It was found that no desired product was obtained in the presence of triethylamine when the starting material 1a was irradiated for 48 h with a high-pressure mercury lamp (365 nm) in acetonitrile under N_2 at room temperature. However, when the 2 $molL^{-1}$ NaOH was used, the photocyclization reaction proceeded smoothly, and the desired quinazoline derivative **2a** was obtained. It was obvious that the photocyclization could be carried out smoothly under stronger base condition. Using above reaction conditions, a series of novel quinazoline derivatives **2a-f** were successfully synthesized in moderate yields using the thiourea derivative **1a-f** (Table 1). It was found that substituent effects were the key factor in reaction yield. The more electron-withdrawing groups connected with quinazoline ring, the higher yields of products were obtained. The reaction yield reached the yield of 44%-55%.

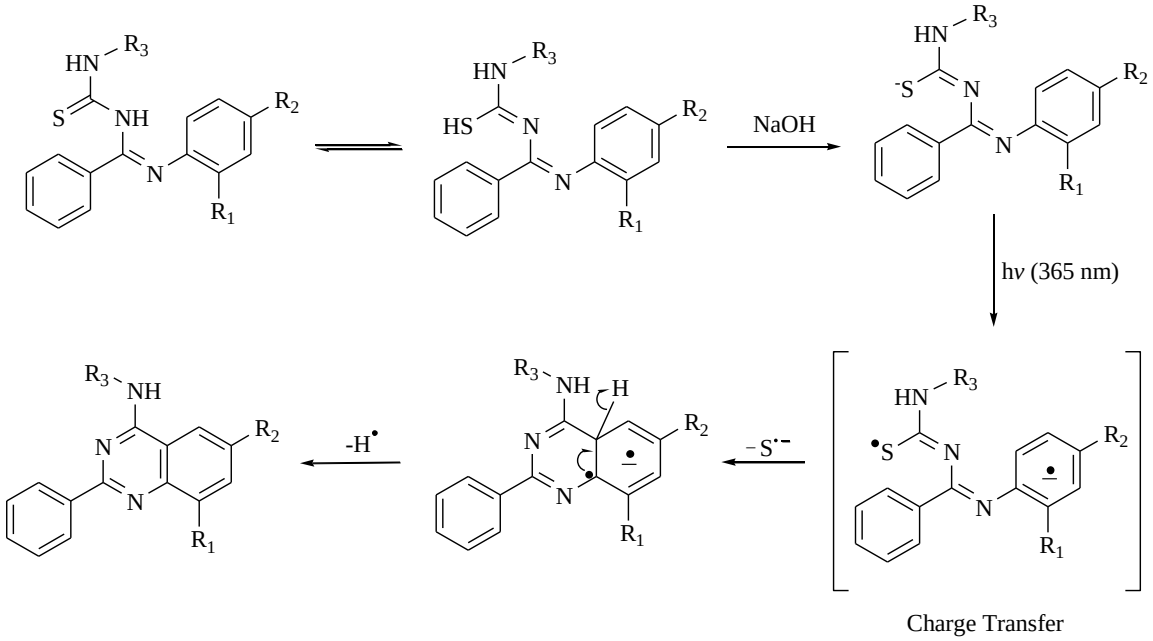
N, *N*'–disubstituted thiourea **1a-f** were respectively added in the mixed solvent of acetontrile and aqueous NaOH, stirred either at room temperature or refluxing for 48 h without ultraviolet light irradiation, only the starting materials were found.In addition, *N*, *N*'–disubstituted thiourea **1a-f** were respectively dissolved in acetontrile without adding aqueous NaOH by ultraviolet light irradiation for 48 h, but no new compound was isolated except for the starting materials. It was shown that the aqueous NaOH and ultraviolet light irradiation were all necessary conditions for the synthesis of the title compounds.

Table 1. Photoproducts of 4-arylamino-2-phenyl-6-substituted-quinazoline **2a-f**

Entry	2	R^1	R^2	R^3	Time[a]	Yield (%)[b]
1	2a	H	H	*p*-methoxyphenyl	5.5	47
2	2b	Me	H	*o*-chlorophenyl	4.5	55
3	2c	Me	H	*p*-methylphenyl	5.5	49
4	2d	Cl	H	*o*-chlorophenyl	4	54
5	2e	Cl	H	*p*-methylphenyl	6	52
6	2f	H	Me	naphthyl	2	44

[a] Time in hours. [b] Isolated yields.

Formation of the quianzoline derivatives from *N*,*N*'–disubstituted thiourea derivatives **1** can be explained by the following mechanism (Scheme 2).



Scheme 2

According to this mechanism, the first step was the formation of anionic thiocarbonyl sulphur of the thioamide bond in basic medium, and the second step was the formation of anionic radical species by photoinduced electron transfer[22] and which was followed by the intramolecularly substitution the hydrogen radical of benzene to obtain the final product.

The structures of all compounds **2a-f** were established on the basis of elemental analysis and spectral data. The IR spcetral data of compounds **2a-f** showed bands at 3430–3440 cm^{-1} and 1520–1540 cm^{-1} due to N-H and C=N, respectively. The ^1H NMR spectra of **2a-f** exhibited a broad singlet in the δ 7.29–8.15 range accounting for amino protons, the region of δ 7.10–9.05

accounted for aromatic protons. In the ^{13}C NMR spectra of synthesized compounds, the signals observed in the region of δ 158–161 and 157–158 accounted for (C-4) and (C-2), respectively.

Conclusions

In conclusion, we have developed a new approach by photochemistry for the synthesis of quinazoline derivatives. A series of novel 4-arylamino-2-phenyl-6-substituted-quinazoline have been synthesized by the irradiation of *N*,*N*'–disubstituted thiourea derivatives in the MeCN/NaOH medium. This synthetic reaction has the advantages of readily available starting materials, mild reaction conditions, and simple manipulations.

Experimental Section

General. The solvent and all reagents used in this study were purchased from commercial suppliers and were used as received. Melting point was taken on a Yanagimoto MP-500 apparatus and uncorrected. IR spectra were measured on a BIO-RAD FTS 3000 spectrometer using KBr disks. The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz and 500 MHz nuclear magnetic resonance spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. EI-MS spectra were measured on a Waters Xevo-TQMS (HPLC-MS). The elemental analysis was performed on FLASH EA1112 elemental analyzer.

General procedure for preparation of 4-Arylamino-2-phenyl-6-substituted-quinazoline (2)
To *N*,*N*'–disubstituted thiourea (0.5 mmol) in a quartz tube was added MeCN (300 mL) and aqueous NaOH (20 mL, 2 $molL^{-1}$). The mixture, deaerated by nitrogen purging for 1 h, was stirred and irradiated under a high-pressure mercury lamp (365 nm) and for given hours. After completion of the reaction (checked by TLC), the reaction mixture was separated, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel with eluting CH_2Cl_2-MeOH (120:1) to give the desired product. The physical and spectra data of the compounds **2a-f** are as follows:
4-(4-Methoxyphenylamino)-2-Phenylquinazoline (2a). Cardinal-red solid, mp 161-163 ˚C. IR (ν_{max}, cm^{-1}): 3430, 1525, 1350. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.86 (s, 3H, OCH_3), 7.00 (dd, J_1 = 2.0 Hz, J_2 = 6.5 Hz, 2H, ArH), 7.36 (s, 1H, NH),7.45-7.59 (m, 4H, ArH), 7.73-7.84 (m, 4H, ArH), 7.96-7.98 (m, 1H, ArH), 8.51-8.53 (m, 2H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm : 55.60, 113.74, 114.22, 120.29, 123.42, 125.95, 128.36, 128.52, 129.20, 130.26, 131.62, 132.81, 138.62, 150.90, 156.54, 157.56, 160.40. MS *m*/*z* (%):328 [M^++1] (100). Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.03; H, 5.24; N, 12.84. Found: C, 77.13; H, 5.07; N, 12.80.

4-(2-Chlorophenylamino)-8-Methyl-2-phenylquinazoline (2b). Colorless needles, mp 133-134 ˚C. IR (ν_{max}, cm^{-1}): 3420, 1523, 1352. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.82 (s, 3H, CH_3), 7.06-7.09 (m, 1H, ArH), 7.40-7.53 (m, 6H, ArH), 7.64-7.66 (m, 1H, ArH), 7.75 (d, *J* 8.0 Hz, 1H, ArH), 8.14 (s, 1H, NH), 8.59-8.61 (m, 2H, ArH), 9.05 (dd, J_1 1.5 Hz, J_2 8.0 Hz, 1H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 17.66, 114.00, 117.76, 122.04, 123.42, 123.65, 125.92, 127.63, 128.41, 128.49, 129.15, 130.24, 133.10, 135.72, 138.02, 138.96, 150.04, 157.23, 158.84. MS *m*/*z* (%):346 [M^++1] (100). Anal. Calcd for $C_{21}H_{16}ClN_3$: C, 73.02; H, 4.67; N, 12.17. Found: C, 73.10; H, 4.65; N, 12.20.

8-Methyl-4-(4-methylphenylamino)-2-phenylquinazoline (2c). White solid, mp 134-136 ˚C. IR (ν_{max}, cm^{-1}): 3430, 1520, 1350. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.39 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 7.38-7.50 (m, 7H, NH, ArH), 7.60-7.65 (m, 2H, ArH), 7.73-7.56 (m, 2H, ArH), 8.59-8.61 (m, 2H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 17.70, 20.95, 113.53, 117.69, 121.24, 125.34, 128.29, 128.51, 129.50, 130.07, 132.80, 133.49, 136.32, 137.85, 139.14, 149.98, 157.66, 159.03. MS *m*/*z* (%):326 [M^++1] (100). Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.19; H, 5.89; N, 12.92. Found: C, 81.08; H, 5.81; N, 12.85.

8-Chloro-4-(2-chlorophenylamino)-2-phenylquinazoline (2d). White solid, mp 181-182 ˚C. IR (ν_{max}, cm^{-1}): 3430, 1520, 1340. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm:, 7.10-7.13 (m, 1H, ArH), 7.43-7.54 (m, 6H, ArH), 7.81 (dd, J_1 1.0 Hz, J_2 8.5 Hz, 1H, ArH), 7.90 (dd, J_1 1.0 Hz, J_2 7.5 Hz, 1H, ArH), 8.16 (s, 1H, NH), 8.60-8.62 (m, 2H, ArH), 8.97 (dd, J_1 1.5 Hz, J_2 = 8.0 Hz, 1H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 115.50, 118.99, 122.34, 123.70, 124.24, 125.98, 127.69, 128.49, 128.79, 129.22, 130.78, 133.12, 134.24, 135.20, 138.21, 147.87, 157.08, 160.62,. MS *m*/*z* (%):366 [M^++1] (100). Anal. Calcd for $C_{20}H_{13}Cl_2N_3$: C, 65.74; H, 3.59; N, 11.51. Found: C, 65.72; H, 3.68; N, 11.40.

8-Chloro-4-(4-methylphenylamino)-2-phenylquinazoline (2e). White solid, mp 109-110 ˚C. IR (ν_{max}, cm^{-1}): 3490, 1540, 1340. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.38 (s, 3H, CH_3), 7.18-7.21 (m, 1H, ArH), 7.29-7.46 (m, 7H, NH, ArH), 7.73 (dd, J_1 1.5 Hz, J_2 8.5 Hz, 1H, ArH), 7.88 (dd, J_1 1.0 Hz, J_2 7.5 Hz, 1H, ArH), 8.07 (dd, J_1 1.0 Hz, J_2 8.0 Hz, 1H, ArH), 8.52-8.54 (m, 2H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 18.18, 115.16, 119.08, 124.24, 125.48, 126.76, 128.36, 128.74, 130.62, 130.78, 132.91, 134.11, 136.51, 138.27, 147.96, 157.98, 160.81. MS *m*/*z* (%):345 [M^++1] (100). Anal. Calcd for $C_{21}H_{16}ClN_3$: C, 73.02; H, 4.67; N, 12.17. Found: C, 73.08; H, 4.72; N, 12.08.

6-Methyl-4-naphthylamino-2-phenylquinazoline (2f). Pale-yellow solid, m.p. 182-184 ˚C. IR (KBr): 3250, 1520, 1340. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.59 (s, 3H, CH_3), 7.38-7.39 (m, 3H, ArH), 7.51-7.74 (m, 4H, ArH), 7.72-7.80 (m, 3H, NH, ArH), 7.92-7.95 (m, 2H, NH, ArH), 8.02-8.04 (m, 1H, ArH), 8.20-8.22 (m, 1H, ArH), 8.34-8.36 (m, 2H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 21.91, 113.80, 119.59, 121.41, 121.68, 125.69, 125.75, 126.05, 126.29, 128.24, 128.34, 128.86, 129.22, 129.99, 133.78, 134.40, 134.92, 136.16, 138.66, 149.67, 158.02, 159.74. MS *m*/*z* (%):345 [M^++1] (100). Anal. Calcd for $C_{25}H_{19}N_3$: C, 83.08; H, 5.30; N, 11.63. Found: C, 83.12; H, 5.24; N, 11.58.

Acknowledgements

This work was supported by the China Postdoctoral Science Foundation funded project (No. 2011M500634), Heilongjiang Province Postdoctoral Science Foundation funded project (No. LBH-Z10241), Research Science Foundation in Technology Innovation of Harbin (No. 2010RFQXS070) and Northeast Agricultural University Doctor Foundation funded project (No. 2009RC22).

References

1. (a) Chilin,A.; Conconi, M. T.; Marzaro, G.; Guiotto, A.; Urbani, L.; Tonus, F.; Parnigotto, P. *J*. *Med*. *Chem*. **2010**, *53*, 1862. (b) Shreder, K. R.; Wong, M. S.; Nomanbhoy, T.; Leventhal, P. S.; Fuller, S. R. *Org*. *Lett*. **2004**, *6*, 3715. (c) Tsou, H. R.; Mamuya, N.; Johnson, B. D.; Reich, M. F.; Gruber, B. C.; Ye, F.; Nilakantan, R.; Shen, R.; Discafani, C.; DeBlanc, R.; Davis, R.; Koehn, F. E.; Greenberger, L. M.; Wang, Y. F.; Wissner, A. *J*. *Med*. *Chem*., **2001**, *44*, 2719. (d) Smaill, J. B.; Rewcastle, G. W.; Loo, J. A.; Greis, K. D.; Chan, O. H.; Reyner, E. L.; Lipka, E.; Showalter, H. D.; Vincent, P. W.; Elliott, W. L.; Denny, W. A. *J*. *Med*. *Chem*., **2000**, *43*, 1380.
2. Amin, K. M.; Kamel, M. M.; Anwar, M. M.; Syam, M.; Khedr, Y. M. *Eur*. *J*. *Med*. *Chem*., **2010**, *45*, 2117.
3. Xu, G. F.; Song, B. A.; Bhadury, P. S.; Yang, S.; Zhang, P. Q.; Jin, L. H.; Xue, W.; Hu, D. Y.; Lu, P. *Bioorg*. *Med*. *Chem*. **2007**, *15*, 3768.
4. Rohini, R.; Reddy, P. M.; Shanker, K.; Hu, A.; Ravinder, V.; *Eur*. *J*. *Med*. *Chem*. **2010**, *45*, 1200.
5. Alagarsamy, V.; Pathak, U. S. *Bioorg*. *Med. Chem*. **2007**, *15*, 3457.
6. Ismail, M. A. H.; Aboul-Enein, M. N. Y.; Abouzid, K. A. M.; Serya, R. A. T. *Bioorg*. *Med*. *Chem*. **2006**, *14*, 898.
7. Kabri, Y.; Azas, N.; Dumètre, A.; Hutter, S.; Laget, M.; Verhaeghe, P.; Gellis, A.; Vanelle, P. *Eur*. *J*. *Med*. *Chem*. **2010**, *45*, 616.
8. Laddha, S. S.; Bhatnagar, S. P. *Bioorg*. *Med*. *Chem*. **2009**, *17*, 6796.
9. Cope, H.; Mutter, R.; Heal, W.; Pascoe, C.; Brown, P.; Pratt, S.; Chen, B. *Eur*. *J*. *Med*. *Chem*. **2006**, *41*, 1124.
10. Nilsson, M.; Belfrage, A. K.; Lindström, S.; Wähling, H.; Lindquist, C.; Ayesa, S.; Kahnberg, P.; Pelcman, M.; Benkestock, K.; Agback, T.; Vrang, L.; Terelius, Y.; Wikström, K.; Hamelink, E.; Rydergård, C.; Edlund, M.; Eneroth, A.; Raboisson, P.; Lin, T. I.; de Kock, H.; Wigerinck, P.; Simmen, K.; Samuelsson, B.; Rosenquist, Å. *Bioorg*. *Med*. *Chem*. *Lett*. **2010**, *20*, 4004.

11. Iino, T.; Sasaki, Y.; Bamba, M.; Mitsuya, M.; Ohno, A.; Kamata, K.; Hosaka, H.; Maruki, H.; Futamura, M.; Yoshimoto, R.; Ohyama, S.; Sasaki, K.; Chiba, M.; Ohtake, N.; Nagata, Y.; Eiki, J.; Nishimura, T. *Bioorg*. *Med*. *Chem*. *Lett*. **2009**, *19*, 5531.
12. Szczepankiewicz, W.; Suwiński, J.; Bujok, R. *Tetrahedron* **2000**, *56*, 9343.
13. Chern, J. W.; Tao, P. L.; Wang, K. C.; Gutcait, A.; Liu, S. W.; Yen, M. H.; Chien, S. L.; Rong, J. K. *J*. *Med*. *Chem*. **1998**, *41*, 3128.
14. (a) Wang, X. B.; Song, A. M.; Dixon, S.; Kurth, M. J.; Lam, K. S. *Tetrahedron Lett*. **2005**, *46*, 427. (b) Okuzumi, T.; Nakanishi, E.; Tsuji, T.; Makino, S. *Tetrahedron* **2003**, *59*, 5603.
15. (a) Chilin, A.; Marzaro, G.; Zanatta, S.; Guiotto, A.; *Tetrahedron Lett*. **2007**, *48*, 3229. (b) G. Li, R. Kakarla, S. W. Gerritz, A. Pendri, and B. Q. Ma, *Tetrahedron Lett*. **2009**, *50*, 6048.
16. Maitraie, D.; Yakaiah, T.; Srinivas, K.; Reddy, G. V.; Ravikanth, S.; Narsaiah, B.; Rao, P. S.; Ravikumar, K.; Sridhar, B. *J*. *Fluorine*. *Chem*. **2006**, *127*, 351.
17. Marzaro, G.; Guiotto, A.; Pastorini, G.; Chilin, A. *Tetrahedron* **2010**, *66*, 962.
18. (a) Wang, M. M.; Dou, G. L.; Shi, D. Q. *J*. *Comb*. *Chem*. **2010**, *12*, 582. (b) Blank, J.; Kandt, M.; Pfeiffer, W. D.; Hetzheim, A.; Langer, P. *Eur*. *J*. *Org*. *Chem*. **2003**, 182.
19. Kumar, V.; Bhargava, G.; Dey, P. D.; Mahajan, M. P. *Synthesis* **2005**, *18*, 3059.
20. Xing, Z. Y.; Zhao, Q.; Fu, Y.; Ye, F. *Chem*. *Heterocycl*. *Comp*. **2011**, *47*, 607.
21. Van den nieuwendijk, A. M. C. H.; Pietra, D.; Heitman, L.; Göblyös, A.; IJzerman, A. P. *J*. *Med*. *Chem*. **2004**, *47*, 663.
22. Senthilvelan, A.; Thirumalai, D.; Ramakrishnan, V. T. *Tetrahedron* **2004**, *60*, 851.

