Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 21 (2010) 782–786
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

A convenient synthesis of quinazoline derivatives *via* cascade imino-Diels-Alder and oxidation reaction

Xue Ming Chen [a,b], Hui Wei [a], Lu Yin [a], Xing Shu Li [a,*]

[a] *School of Pharmaceutical Science, Sun Yat-Sen University, Guangzhou 510006, China*
[b] *National Technical Center, Shenzhen Neptunus Bioengineering Holdings Co., Ltd., Shenzhen 518057, China*

Received 15 October 2009

Abstract

Quinazoline derivatives were synthesized from α-iminoesters *via* a cascade imino-Diels-Alder and then oxidation reaction catalyzed with $CuBr_2$. This method provided a new strategy for preparing quinazoline derivatives which may be useful in the synthesis of heterocyclic intermediates.

Keywords: Quinazolines; α-Iminoesters; Imino-Diels-Alder reaction; $CuBr_2$

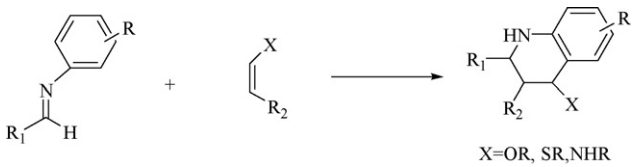
Quinazoline derivatives are endowed with a large spectrum of biological activities, including remarkable anti-inflammatory activity [1], anti-cancer [2], antiviral [3] and antitubercular activity [4]. For example, gefitinib (Iressa®) and erlotinib hydrochloride (Tarceva®), which are potent inhibitors of epidermal growth factor receptor-tyrosine kinase enzymes [5] with the structure of central quinazoline units, were approved by FDA for the treatment of non-small-cell lung cancer [6]. Traditional preparations of quinazoline derivatives, including Niementowski synthesis [7], Bischler synthesis [8], Riedel synthesis [9] and modified Duff synthesis [10], suffer from limited source of starting material. From practical standpoints, it is desirable to develop new methods for the synthesis of these useful compounds.

On the other hand, imino-Diels-Alder reaction [11] that involved coupling of imines with electron rich olefins has emerged as a powerful tool for the synthesis of tetrahydroquinolines [12]. Cycloadditions of arylimines to dienophiles including enolates, thioenolates, enamines, and dienes such as cyclopentadiene and cyclohexadiene are well documented in literature (Scheme 1) [13]. Moreover, α-iminoesters have been used in synthetic organic chemistry for many years [14], such as the preparation of amino acids [15,16] and their derivatives [17]. Recently, we have synthesized a series of new compounds such as tetrasubstituted 3-alkynylpyrroles [18], β-amino esters [19], 1,4-dihydropyridines [20], chiral tricarboxylate [21] and imidazolin-4-ones [22] by using α-iminoesters as starting material. Herein, we disclose a convenient synthesis of quinazoline derivatives from α-iminoesters.

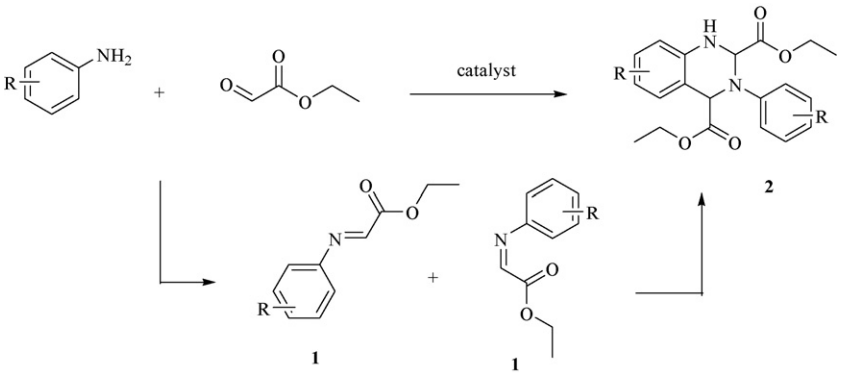
We chose aniline and ethyl glyoxalate as the substrates, and hypothesized those two molecules of α-iminoesters, which were produced *in situ* by condensation of aniline and ethyl glyoxalate, could form quinazoline derivatives **2** *via*

* Corresponding author.
E-mail address: lixsh@mail.sysu.edu.cn (X.S. Li).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2010.03.003



Scheme 1. Cycloadditions of arylimines to dienophiles.



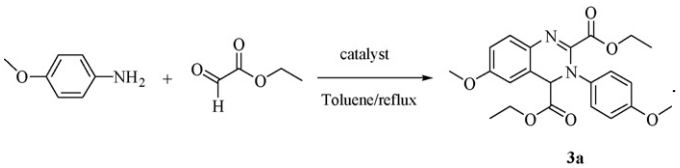
Scheme 2. Strategy of imino-Diels-Alder reaction for the synthesis of quinazoline derivatives.

imino-Diels-Alder reaction [23,13d,e], originally described by Povarov et al. (Scheme 2). However, no other product but aldimine was obtained when the reaction was carried out in toluene under refluxing for 24 h.

Efforts then were focused to find appropriate catalysts and reaction conditions to perform the proposed strategy. In the preliminary study for finding effective catalyst, we chose Lewis acids, such as $FeCl_3$, $AlCl_3$, $CuCl_2$, $Cu(OAc)_2$, $AgNO_3$, $Cu(OTf)_2$, $CuBr_2$, $ZnBr_2$, and $Sc(OTf)_3$ as candidates for this screening test (Table 1).

It was interesting that quinazoline **3a**, rather than **2**, was obtained in 76% yield when $CuBr_2$ was used as the catalyst. Other catalysts were also tested for the reaction, $AlCl_3$ and $Cu(OTf)_2$ gave product **3a** in 50% and 70% yields,

Table 1
Synthesis of quinazolines by various catalysts.[a]

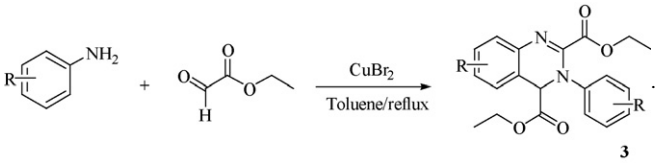


3a

Entry	Catalyst	Solvent	Yield (%)[b]
1	$FeCl_3$	Toluene	ND
2	$AlCl_3$	Toluene	50
3	$CuCl_2$	Toluene	Trace
4	$AgNO_3$	Toluene	ND
5	$Cu(OAc)_2$	Toluene	ND
6	$ZnBr_2$	Toluene	Trace
7	$Sc(OTf)_3$	Toluene	Trace
8	$Cu(OTf)_2$	Toluene	70
9	$CuBr_2$	Toluene	76
10	$CuBr_2$	DMSO	72
11	$CuBr_2$	DMF	Trace

[a] Reaction conditions: amine (1.0 mmol), ethyl glyoxalate (1.2 mmol), and catalyst (0.1 mmol).
[b] Isolated yield.

Table 2
Synthesis of quinazoline derivatives via cascade Povarov-oxidation reaction.[a]



3

Entry	R	Product	Yield (%)[b]
1	*p*-CH_3O	**3a**	76
2	*p*-CH_3	**3b**	70
3	*p*-Cl	**3c**	61
4	*p*-Br	**3d**	55
5	*m*-CH_3	**3e**	63
6	*m*-Cl	**3f**	51
7	*m*-CH_3O	**3h**	Polymer
8	*o*-Cl	**3j**	Polymer
9	*o*-CH_3	**3k**	Polymer
10	H	**3i**	Trace

[a] Reaction conditions: amine (1.0 mmol), ethyl glyoxalate (1.2 mmol), and $CuBr_2$ (0.1 mmol).
[b] Isolated yield.

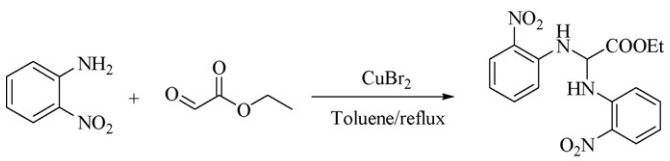
respectively. On the other hand, $CuCl_2$, $ZnBr_2$ and $Sc(OTf)_3$ only gave trace quinazoline **3a** in the same reaction conditions. Other factors such as solvent and temperature were also studied with $CuBr_2$ as the catalyst. Xylene provided 72% yield but DMF and DMSO gave either low yield or byproducts. Very low yields were obtained when the reactions were performed at a lower temperature.

In order to extend the scope of this reaction, other amines were tested at refluxing with toluene as the optimal solvent. The results listed in Table 2 [24] indicated that aromatic amines with electron-donating group on the *para*-position of the phenyl ring, such as methoxy, methyl, chloride or bromide group afforded corresponding quinazoline derivatives with good yields from 55% to 76% (entries 1–4, Table 2). When the amine was *meta*-methyl or *meta*-chloride aniline, the yield was also good (entries 5–6, Table 2). However, amines derived from *meta*-methoxy, *ortho*-chloride and *ortho*-methyl aniline did not provide the desired products (entries 7–9, Table 2).

It was unexpected that amine **4**, ethyl 2,2-bis(2-nitrophenylamino)acetate, rather than quinazoline derivative, was isolated in 61% yield for *o*-nitroaniline (Scheme 3). The single-crystal of compound **4** was obtained and the structure was characterized by X-ray diffraction analysis (Fig. 1).

We also carried out the reaction with the preformed α-iminoester **1** as the substrates at the same reaction conditions as that of amines and ethyl glyoxalate (Table 3). The same products and yields indicated that α-iminoester is the sole intermediate of the reaction.

In summary, we have developed a simple synthetic protocol for quinazoline derivatives *via* imino-Diels-Alder reaction which occurred between two α-iminoesters. The use of simple and cheap materials and catalyst, as well as mild reaction conditions make this strategy an alternative to these useful compounds. Further efforts on expanding the scope of the cascade Povarov-oxidation reaction, reaction mechanism and the enantioselective synthesis of this class of quinazoline derivatives are in progress.



4 (61%yield)

Scheme 3. The reaction of *o*-nitroaniline and ethyl glyoxalate.

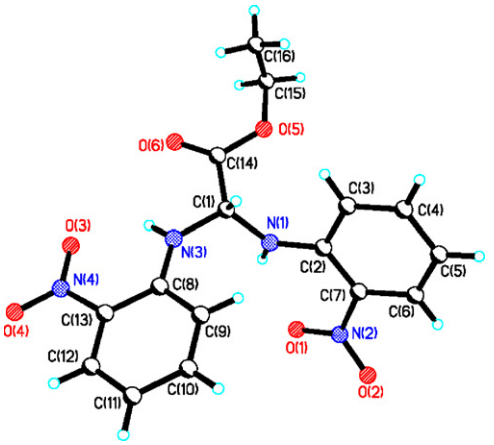
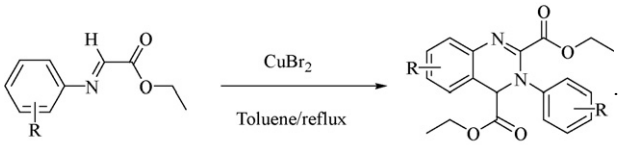


Fig. 1. ORTEP presentation of ethyl 2,2-bis(2-nitrophenylamino)acetate **4** at 50% probability (CCDC719014).

Table 3
Synthesis of quinazoline derivatives from imines.[a]



3

Entry	R	Product	Yield (%)[b]
1	*p*-CH_3O	**3a**	79
2	*p*-CH_3	**3b**	75
3	*p*-Cl	**3c**	63
4	*p*-Br	**3d**	54
5	*m*-CH_3	**3e**	66
6	*m*-Cl	**3f**	52

[a] Reaction conditions: imine (1.0 mmol), $CuBr_2$ (0.1 mmol).
[b] Isolated yield.

Acknowledgment

We thank the financial support from National Natural Science Foundation of China (No. 20972198).

References

[1] (a) A.C. Tinker, H.G. Beaton, N.B. Smith, et al. J. Med. Chem. 46 (2003) 913;
(b) G.M. Buckley, N. Davies, H.J. Dyke, et al. Bioorg. Med. Chem. Lett. 15 (2005) 751.
[2] (a) A.E. Wakeling, S.P. Guy, J.R. Woodburn, et al. Cancer Res. 62 (2002) 5749;
(b) L.F. Hennequin, J. Allen, J. Breed, et al. J. Med. Chem. 49 (2006) 6465.
[3] (a) T.C. Chien, C.S. Chen, F.H. Yu, et al. Chem. Pharm. Bull. 52 (2004) 1422;
(b) T. Herget, M. Freitag, M. Morbitzer, et al. Antimicrob. Agents Chemother. 48 (2004) 4154.
[4] (a) K. Waisser, J. Gregor, H. Dostal, et al. Farmaco 56 (2001) 803;
(b) J. Kunes, J. Bazant, M. Pour, et al. Farmaco 55 (2000) 725.
[5] (a) D.W. Fry, A.J. Kraker, A. McMichael, et al. Science 265 (1994) 1093;
(b) A.J. Bridge, Chem. Rev. 101 (2001) 2541.
[6] R.S. Herbst, M. Fukuoka, J. Baselga, Nat. Rev. Cancer 4 (2004) 956, and references cited therein.
[7] S.J. Niementowski, Prakt. Chem./Chem. -Ztg. 51 (1895) 564.
[8] A. Bischler, Ber 24 (1891) 506.

[9] A. Riedel, German Patent 174,941 (1905).
[10] G. Marzaro, A. Chilin, G. Pastorini, et al. Org. Lett. 8 (2006) 255.
[11] L.S. Povarov, Russ. Chem. Rev. 36 (1967) 656.
[12] S. Reymond, J. Cossy, Chem. Rev. 108 (2008) 5359.
[13] Recent examples:
(a) A. DiSalvo, M.V. Spanedda, M. Ourevich, et al. Synthesis (2003) 2231;
(b) S. Hermitage, J.A.K. Howard, D.J.R.G. Prichard, et al. Org. Biomol. Chem. 2 (2004) 2451;
(c) P.J. Stevenson, M. Nieuwenhuyzen, D. Osborne, Arkivoc (2007) 129;
(d) T. Hosokawa, A. Matsumura, T. Katagiri, et al. J. Org. Chem. 73 (2008) 1468;
(e) M.J. Alves, N.G. Azoia, A.G. Fortes, Tetrahedron 63 (2007) 727.
[14] T. Andrewe, H. Ahmedm, L. Thomas, Acc. Chem. Res. 36 (2003) 10.
[15] S.M. Weinreb, Top. Curr. Chem. 190 (1997) 131.
[16] R.M. Borzilleri, S.M. Weinreb, Synthesis (1995) 347.
[17] S.D. Joshua, C.K. Marisa, Chem. Soc. Rev. 37 (2008) 1166.
[18] X.M. Chen, L. Hou, X.S. Li, Synlett 5 (2009) 828.
[19] X.M. Chen, X.S. Li, A.S.C. Chan, Chin. Chem. Lett. 20 (2009) 407.
[20] X.M. Chen, X.G. Huang, Y.Y. Chen, et al. Lett. Org. Chem. 6 (2009) 213.
[21] X.G. Huang, X.M. Chen, Y.Y. Chen, et al. Tetrahedron: Asymm. 19 (2008) 2529.
[22] X.M. Chen, Y.Y. Chen, X.S. Li, Helv. Chim. 8 (2009) 1550.
[23] (a) P. Buonora, J.C. Olsen, T. Oh, Tetrahedron 57 (2001) 6099;
(b) J. Zhang, C.J. Li, J. Org. Chem. 67 (2002) 3969;
(c) A. Bongini, M. Panunzio, E. Bandini, et al. J. Org. Chem. 62 (1997) 8911.
[24] General procedure for the synthesis of quinazoline derivatives: In a 10 mL round-bottomed flask, amine (1.0 mmol), ethyl glyoxalate (1.2 mmol), $CuBr_2$ (0.1 mmol) and toluene (15 mL) were added. The mixture was stirred for 5 days at refluxing. The reaction was monitored by TLC. After the reaction was completed, toluene was removed under reduced pressure, the crude product was purified by flash column chromatography (1:5 ethyl acetate/petroleum ether as eluent) to afford the desired quinazoline product. All the products were characterized by ^{1}H NMR and ^{13}C NMR, and the selected data: diethyl 6-methoxy-3-(4-methoxyphenyl)-3,4-dihydroquinazoline-2,4-dicarboxylate (**3a**): yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, 3H, J = 6.9 Hz), 1.23 (t, 3H, J = 6.9 Hz), 3.78 (s, 3H), 3.79 (s, 3H), 4.19 (m, 4H), 5.30 (s, 1H), 6.72 (d, 1H, J = 3.0 Hz), 6.85 (m, 3H), 7.05 (dd, 2H, J = 6.9 Hz, J = 2.4 Hz), 7.33 (d, 1H, J = 2.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.16, 14.49, 55.90, 62.36, 64.18, 111.67, 114.73, 115.20, 121.41, 125.31, 127.45, 133.68, 136.85, 145.88, 158.25, 158.82, 162.63, 169.97. HRMS m/z calcd. for $C_{22}H_{24}N_2O_6$ (M^+): 412.1629, found: 412.1633.