Traceless Synthesis of Quinazoline-2,4-diones By Curtius Rearrangement Reaction using Poly(ethylene glycol) as Soluble Polymeric Support

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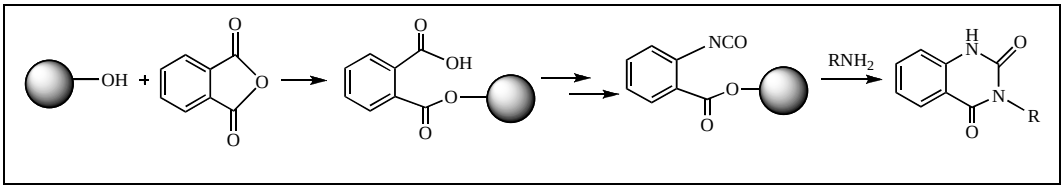

We have developed an efficient method to synthesize various quinazoline-2,4-diones using poly-(ethylene glycol) as soluble polymeric support. The procedure of this reaction included: formation of acyl azide, efficient Curtius rearrangement, nucleophlic addition with amines to produce ureas, cyclization and concurrent cleavage of the resulted six-membered heterocycle from PEG-support in excellent yields. This method is mild and manipulation is easy.

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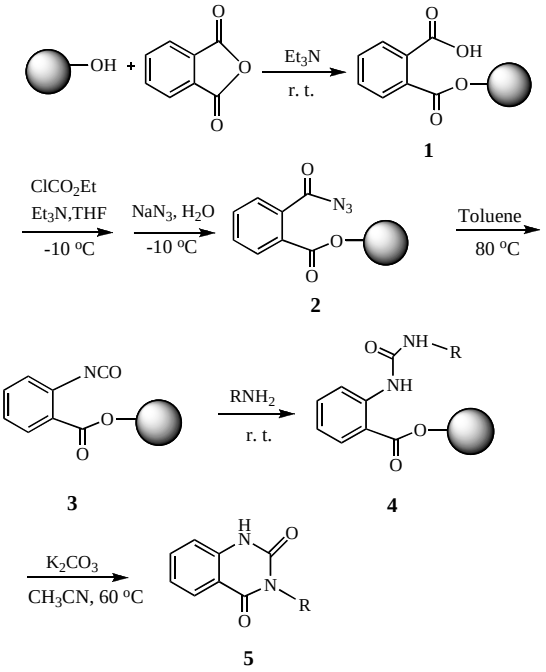
INTRODUCTION

Quinazoline-2,4-dione derivatives have attracted interest of pharmaceutical researchers and synthetic chemists because of their versatile pharmacological activities [1], which involve sedative and antihypotensive activites, as well as anticonvulsant activity against electroshock [2]. Moreover they show useful antiinflammatory property and cause vasodilatation in animals [3]. Because of its important application in medicine, various methods have been developed to synthesize quinazoline-2, 4-diones [4], including solid phase organic synthesis [5].

In recent years, synthesis of small organic molecules on soluble polymeric supports has become a significant field in combinatorial chemistry [6]. It combines the advantages of conventional solution chemistry (high reactivity, lack of diffusion phenomena and easy analysis) and solid phase organic synthesis (use of excessive reagents, easy isolation and purification of products) [7]. Up to date, the synthesis of quinazoline-2,4-diones on soluble polymeric support has not been reported. Based on our experiences in the combinatorial synthesis of heterocyclic compounds on soluble polymeric support [8], we reported herein the novel synthetic approach of quinazoline-2,4-diones using PEG as soluble polymeric support by Curtius rearrangement reaction, which is shown in Scheme 1

Scheme 1



RESULTS AND DISCUSSION

Considering the balance between loading capacity and solubility profile of the resulting polymer-bound derivatives, we chose PEG (MW 3400) as soluble polymeric support in synthesis of quinazoline-2,4-diones. As shown in Scheme 1, PEG reacted with phthalic anhydride using triethylamine as base in dry CH_2Cl_2 at r.t. to quantitatively give PEG-bound phthalate ester **1**. In this step, PEG act both as soluble polymeric support and protective group for carboxylic acid group. The reaction proceeded to completion as monitored by the disappearance of the hydroxy at 3465 cm^{-1} and appearance of the carboxylic acid and PEG-bound ester at 1680 cm^{-1} and

1726 cm^{-1} in IR spectrum. Compound **1** was treated with ethyl chloroformate in anhydrous THF in the presence of triethylamine at -10 °C, and then a solution of sodium azide in water, was added dropwise. After another 3 h at -10 °C, the system gave PEG-bound acyl azide **2** with the absorption at 2137 cm^{-1} for acyl azide. The reaction proceeded efficiently, for PEG itself was a very good phase transfer catalyst and avoiding using other PTC [9]. Compound **2** was readily converted to PEG-bound isocyanate **3** in toluene at 80 °C by Curtius rearrangement reaction. The appearance of absorption at 2255 cm^{-1} was clear evidence for the formation of isocyanate. Compound **3** was partioned into several segments and reacted with a series of primary amines at r.t. in parallel to give **4**. A very efficient cleavage from PEG-bound urea **4** using K_2CO_3 in acetonitrile provided the corresponding crude product **5**, which was purified by recrystallization from ethyl ether or column chromatography.

In order to obtain a wide diversity of quinazoline-2,4-diones, a variety of primary amines were employed. Aliphatic amines gave good results (in high purity and good yields), while aromatic amines and highly-blocked amines such as *t*-butyl amine and cyclohexylamine failed to produce the desired product.

It is worthy of noting that the reaction was easily carried out using PEG as soluble polymeric support, protective group and phase transfer catalyst in mild conditions with excellent yields. The polymer-supported products of each step can be easily isolated and purified by simple precipitating, which can remove the unreacted materials and by-products by washing with cold Et_2O, avoiding tedious work-up procedures in contrast to conventional solution reaction [11,12]. The purity of intermediate products was easily detected by TLC analysis to observe whether the lower molecular reagent disappeared or not. And the configuration of PEG-bound product was readily analyzed by ^1H NMR and IR without detaching material from the polymeric support in each step of the sequences in contrast to insoluble polymers [5].

In conclusion, we have successfully developed an elegant and efficient approach to synthesis of quinazoline-2,4-diones using PEG as soluble polymeric support, and meanwhile PEG act as monoprotection group and phase transfer catalyst. This method was simple, the reaction conditions were mild and the yields were excellent.

EXPERIMENTAL

All organic solvents and base were dried by standard methods. PEG and PEG-bound compounds were melted at 80 °C in vacuum for 30 min before use to remove traces of moisture. Melting points were measured on a WRS-1A digital melting point apparatus. IR spectra were recorded on an IR-spectrum one (PE) spectrometer. ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on Finnigan LCQ DUO MS system. Element analysis were determined by a VarioEL III(Germany) analyzer.

Preparation of PEG-bound phthalate ester (1). Phthalic anhydride (1.74 g, 11.76 mmol) and triethylamine(1.64 mL, 11.76 mmol) was added to a solution of PEG (10.0 g) in dry CH_2Cl_2 (30 mL). The mixture was stirred overnight at rt. After evaporation of the solvent at reduced pressure, the residue was precipitated with cold Et_2O (400 mL). The precipitate was then collected on a sintered glass funnel and thoroughly washed with cold Et_2O (3×50 mL) and dried under vacuum to give **1** (10.40 g, 99%). IR (NaCl): CO 1726(s) cm^{-1}. ^1H NMR: δ 3.4-3.7 (m, 4n-O(CH_2CH_2)$_n$O-); 7.71-8.23(m, 4H, H_{ph}), 11.0(s, 1H, COOH)

Preparation of PEG-bound acyl azide (2). To a solution of **1** (10.40 g) in dry THF (50 mL) at -10 °C was added dropwise triethylamine(1.64 mL, 11.76 mmol) over 30 min, then ethyl chloroformate (1.16 mL, 11.76 mmol) over 30 min, the mixture was stirred at -10 °C for 1 h. Then a solution of sodium azide (0.77 g, 11.76 mmol) in water (28 mL) was added dropwise, continued stirring at -10 °C for 3 h. After evaporating THF, the aqueous phase was extracted with CH_2Cl_2 (3×30 mL), the combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, concentrated and precipitated with cold Et_2O (400 mL). The precipitate was collected by filtration, washed with cold Et_2O (3×50 mL) and dried under vacuum to give **2** (9.6 g, 92.3%). IR (NaCl): CO 1726(s), CON_3 2137(s) cm^{-1}. ^1H NMR:δ 3.41-3.72 (m, 4nH, -O(CH_2CH_2)$_n$O-), 7.51-8.13(m, 4H, H_{ph}).

Preparation of PEG-bound isocyanate (3). The PEG-bound acyl azide **2** (9.6 g) was stirred in toluene (40 mL) at 80 °C for 4 h, after evaporation of toluene to give the clean isocyanate **3** (9.4 g, 93.8%) without purification for further reaction. IR (NaCl): CO 1726 (s), NCO 2255 (m) cm^{-1}.

General procedure preparation of PEG-bound urea (4). The mixture of **3** (4.0 g) and aliphatic amines (2.5 mmol) was stirred in dry CH_2Cl_2 (30 mL) at r.t. for 7 h. After evaporation of the solvent at reduced pressure, the residue was precipitated with cold Et_2O (250 mL), filtered, washed with cold Et_2O (3×50 mL) and dried under vacuum to give **4.**

Preparation of quinazoline-2, 4-dione (5). The appropriate urea derivatives **4** were dissolved in acetonitrile (30 mL), then K_2CO_3 was added and the mixture was stirred at 60 °C for 6 h. After removing acetonitrile, the residue was redissolved in a small amount of CH_2Cl_2, the detached PEG was precipitated by adding cold Et_2O and removed by filtering. Then, the combined filtrate was evaporated to give crude product, which was purified by recrystallization from ethyl ether or column chromatography on silica gel (EtOAc-*n*-hexane, 1:4) to give desired pure product **5**.

3-Benzylquinazoline-2,4(1*H*,3*H*)-dione (5a). This compound was obtained as a white solid in 92% yield by recrystallization from ethyl ether. mp 226-226.4 °C (mp 227, lit. [10]). IR: CONH 1658(s), CO 1709(s), NH 3186(m) cm^{-1}; ^1H NMR: δ 5.29(s, 2H, NCH_2Ar), 7.07(d, J=7.8Hz, 1H, H_{ph}), 7.23-7.32(m, 4H, H_{ph}), 7.53-7.63(m, 3H, H_{ph}), 8.15(d, J=8.4Hz, 1H, H_{ph}), 10.26(s, 1H, NH); ^{13}C NMR: δ NCH_2 44.4, 114.8, 115.2, 123.7, 127.9, 128.7(2C), 128.7 (2C), 129.1, 135.4, 137.0, 138.7, 152.3(CO), 162.6(CO); MS: m/e 253 [M^++H]. *Anal.* Calcd. For $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. .Found: C, 71.36; H, 4.82; N, 11.15;

3-(2-Phenylethyl)quinazoline-2,4(1*H*,3*H*)-dione (5b). This compound was obtained as a white solid in 90% yield by recrystallization from ethyl ether. mp 172-173 °C (mp 173-175, lit.[11]). IR: CONH 1649(s), CO 1712(s), NH 3190(m) cm^{-1}; ^1H NMR: δ 2.87-3.04 (m, 2H, CH_2Ar), 4.32 (t, J=7.8Hz, 2H, NCH_2), 7.12(d, J=8.4Hz, 1H, H_{ph}), 7.21-7.27 (m, 3H, H_{ph}), 7.31-7.65(m, 4H, H_{ph}), 8.15(d, J=8.4Hz, 1H, H_{ph}), 10.24 (s, 1H, NH); ^{13}C NMR: δ CH_2 34.5, NCH_2 42.8, 115.1, 115.5, 119.7, 123.9, 127.0, 128.8 (2C), 129.0(2C), 129.4, 135.5, 139.0, 152.4(CO), 162.7(CO); MS: m/e 267 [M^++H]. Anal. Calcd. For $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.18; H, 5.33; N, 10.60.

3-(1-Phenyl ethyl) quinazoline-2,4(1*H*,3*H*)-dione(5c). This compound was obtained as a white solid in 88% yield. mp 288-289 °C (mp 289-292, lit. [11]). IR: CONH 1652 (s), CO 1714(s), NH 3194(m) cm^{-1}; ^1H NMR: δ 1.96(d, J=7.2Hz, 3H, CH_3), 5.29(m, 1H, $NCHCH_3$), 6.86(d, J=7.8Hz, 1H, H_{ph}), 7.20-7.35 (m, 4H, H_{ph}), 7.48-7.59(m, 3H, H_{ph}), 8.11 (d, J=7.8Hz, 1H, H_{ph}), 10.02(s, 1H, NH); ^{13}C NMR: δ CH_3 18.5, NCH 49.8, 114.9, 115.1, 120.4, 123.6, 127.8, 128.145(2C), 129.0 (2C), 135.6, 139.4, 141.25, 152.9(CO), 162.7(CO); MS: m/e 267 [M^++H]. *Anal*. Calcd. For $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52; Found: C, 72.13; H, 5.26; N, 10.58.

3-(2-Furylmethyl) quinazoline-2,4(1*H*,3*H*)-dione (5d). This compound was obtained as a white solid in 87% yield. mp 113.4-114.2 °C. IR: CONH 1716(s), CO 1772(s), NH 3504(m) cm^{-1}; ^1H NMR: δ 4.86(s, 2H, NCH_2), 6.29~6.31(t, J=3.0Hz, 1H, CHC), 6.34(d, J=3.0Hz, 1H, CHCHO), 7.33(d, J=1.2Hz, 1H, OCH), 7.71-7.73(m, 2H, H_{ph}), 7.85-7.87(m, 2H, H_{ph}), 10.02 (s, 1H, NH); ^{13}C NMR: δ NCH_2 34.2, 108.7, 110.4, 121.7, 123.4, 124.5, 127.7, 132.0, 134.1, 142.4, 149.2, 152.5(CO), 167.6(CO); MS: m/e 243 [M^++H]. *Anal*. Calcd. For $C_{13}H_{10}N_2O_2$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.38; H, 4.20; N, 11.58.

3-Heptyl quinazoline-2,4(1*H*,3*H*)-dione(5e). This compound was obtained as a white solid in 90% yield. mp 136.2-136.8 °C. IR: CONH 1638(s), CO 1726(m), NH 3196(m) cm^{-1}; ^1H NMR: δ 0.88(t, J=7.2Hz, 3H, CH_3), 1.21-1.41 (m, 10H, $(CH_2)_5$), 4.07 (t, J=7.8Hz, 2H, NCH_2), 7.09 (d, J=7.2Hz, 1H, H_{ph}), 7.23-7.27(m, 1H, H_{ph}), 7.60-7.63 (m, 1H, H_{ph}), 8.14(d, J=7.8Hz, 1H, H_{ph}), 9.52 (s, 1H, NH); ^{13}C NMR: δ CH_3 14.1, CH_2 22.8, CH_2 26.5, CH_2 27.3, CH_2 30.8, CH_2 32.1, NCH_2 42.9, 114.3, 114.7, 123.3, 127.9, 133.9, 138.8, 151.4(CO), 162.3(CO); MS: m/e 261 [M^++H]. *Anal*. Calcd. For $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.17; H, 7.79; N, 10.81.

3-Hexyl quinazoline-2,4(1*H*,3*H*)-dione(5f). This compound was obtained as a white solid in 90% yield. mp 149.9-150.5 °C. IR: CONH 1638(s), CO 1726(s), NH 3196 (m)cm^{-1}; ^1H NMR: δ 0.89(t, J=7.8Hz, 3H, CH_3), 1.32-1.42(m, 8H, $(CH_2)_4$), 4.07(t, J=7.8Hz, 2H, NCH_2), 7.05 (d, J=7.2Hz, 1H, H_{ph}), 7.22-7.26(m, 1H, H_{ph}), 7.59-7.61(m, 1H, H_{ph}), 8.14(d, J=7.8Hz, 1H, H_{ph}), 9.19 (s, 1H, NH); ^{13}C NMR: δ CH_3 14.0, CH_2 22.5, CH_2 26.6, CH_2 27.8, CH_2 31.5, NCH_2 41.1, 114.6, 114.7, 123.3, 128.5, 134.9, 138.3, 151.4(CO), 162.3 (CO); MS: m/e 247 [M^++H]. *Anal*. Calcd. For $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.28; H, 7.35; N, 11.43.

3-Butyl quinazoline-2, 4(1*H*,3*H*)-dione(5g). This compound was obtained as a white solid in 88% yield. mp 153-155.2 °C (mp: 156, lit.[10]). IR: CONH 1637(s), CO 1725(s), NH 3196(m)cm^{-1}; ^1H NMR: δ 0.87(t, J=7.8Hz, 3H, CH_3), 1.12~1.18 (m, 2H, CH_2), 1.53-1.60(m, 2H, CH_2), 3.41(t, J=7.2 Hz 2H, NCH_2), 7.10(d, J=7.8Hz, 1H, H_{ph}), 7.22-7.28 (m, 1H, H_{ph}), 7.47-7.76(m, 1H, H_{ph}), 7.99(m, 1H, H_{ph}), 10.28(s, 1H, NH); ^{13}C NMR: δ CH_3 14.1, CH_2 20.6, CH_2 29.9, NCH_2 42.7, 118.7, 119.3, 124.9, 129.9, 134.3, 138.9, (CO) 151.1, (CO)163.0; MS: m/e 219 [M^++H]. *Anal*. Calcd. For $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.00; H, 6.42; N, 12.87.

3-*sec*-Butylquinazoline-2,4(1*H*,3*H*)-dione (5h). This compound was obtained as a white solid in 86% yield. mp 133.1-134.2 °C (mp: 131-132, lit.[12]). IR: CONH 1660(s), CO 1712(m), NH 3197(m) cm^{-1}; ^1H NMR: δ 0.92(t, J=7.8Hz, 3H, CH_3), 1.56(d, J=7.2Hz, 3H, CH_3), 1.90-2.24(m, 2H, CH_2), 5.11(d, J=6.6Hz, 1H, NCH), 7.10(d, J=8.4Hz, 1H, H_{ph}), 7.21-7.26(m, 1H, H_{ph}), 7.59-7.62(m,1H, H_{ph}), 8.12(d, J=7.8Hz, 1H, H_{ph}), 10.55(s, 1H, NH); ^{13}C NMR : δ CH_3 11.4, CH_3 17.8, CH_2 26.3, NCH 51.6, 114.7, 114.8, 123.2, 128.4, 134.8, 138.8, 152.7(CO), 162.9(CO); MS: m/e 219 [M^++H]. *Anal*. Calcd. For $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84; Found: C, 66.01 ; H, 6.44; N, 12.86.

3-Propylquinazoline-2,4(1*H*,3*H*)-dione (5i). This compound was obtained as a white solid in 84% yield. mp 186.3-186.8 °C (mp: 186-187, lit.[10]). IR: CONH 1638(s), CO 1722(s), NH 3197(m)cm^{-1}; ^1H NMR: δ 1.10 (t, J=7.2Hz, 3H, CH_3), 1.65-1.77(m, 2H, CH_2), 4.06 (t, J=7.2Hz, 2H, NCH_2), 7.12(d, J=7.8Hz, 1H, H_{ph}), 7.23-7.27(m, 1H, H_{ph}), 7.61-7.73(m, 1H, H_{ph}), 8.14(d, J=7.8Hz, 1H, H_{ph}), 10.01 (s, 1H, NH); ^{13}C NMR :δ CH_3 10.3, CH_2 22.1, NCH_2 46.4, 114.3, 115.2, 123.3, 126.7, 134.8, 138.1, 148.5(CO), 160.5(CO); MS: m/e 205 [M^++H]. *Anal*. Calcd. For $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72; Found: C, 64.71; H, 5.95; N, 13.77.

3-Methylquinazoline-2,4(1*H*,3*H*)-dione(5j). This compound was obtained as a white solid in 78% yield. mp 242-243.4 °C (mp 241, lit.[10]). IR: CONH 1640(s), CO 1723(s), NH 3199 (m) cm^{-1}; ^1H NMR: δ 3.19(d, J=6.0Hz, 3H, NCH_3), 7.71-7.72(m, 2H, H_{ph}), 7.83-7.86 (m, 2H, H_{ph}), 10.21 (s, 1H, NH); ^{13}C NMR: δ CH_3 29.6, 114.2, 121.7, 123.0, 128.5, 134.9, 138.3, 151.4(CO), 161. (CO)2; MS: m/e 177 [M^++H]. *Anal*. Calcd. For $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.33; H, 4.60 ; N, 15.92.

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REFERENCES

[1] Langloisl, M.; Soulierl, J. L.; Rampillonl, V.; Gallaisl, C.; Brkmontl, B. and Shenl, S. *Eur. J. Med. Chem.* **1994**, *29*, 925.

[2] (a) S. Hayao, H. J. Havera and H. E. Hartzler, *J. Med. Chem.* **1965**, *8*, 807; (b) D. G. Wenzel, *J. Am. Pharm. Assoc.* **1955**, *44*, 550.

[3] Haver, H. J. And Vidrio, H. J. *J. Med. Chem.* **1979**, *22*, 1548.

[4] (a) Michael, C. W.; Robert, H. S.; Anthony, J. F. and Robert, L. W. *Org. Lett.* **2006**, *8*, 5089; (b) Rivero, I. A.; Espinoza, K. and Somanathan, R. *Molecules.* **2004**, *9*, 609; (c) Javad, A.; Ali, A. M. and Ali, R. K. *Synth. Comm.* **2003**, *33*, 415; (d) Dominik, S.; Heiko, G. and Willi, B. *Helevical, Chime Acta.* **2003**, *188*, 86; (e) George, M. B.; Natasha,D.; Hazel, J. D. and Alan, F. H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 751; (f) Takumi, M.; Toshiyuki, I. and Yoshio, I. *Tetrahedron Lett.* **2004**, *45*, 7073; (g) Azizian, J.; Mehrdad, M.; Jadidi, K. and Sarrafi, Y. *Tetrahedron Lett.* **2000**, *41*, 5265.

[5] (a) Gouilleux, L.; Fehrentz, J. A.; Winternitz, F. and Martine, J. *Tetrahedron Lett.* **1996**, *37*, 7031; (b) Mikhail, F. G.; Hon, C. H.; Eric, M. G. and Dinesh, V. P. *Tetrahedron Lett.* **1997**, *38*, 1729 ; (c) Hui, S.; Marcus, C.; Tong, S. J.; Zhang, H. S. and Arlindo, L. C. *Tetrahedron Lett.* **1998**, *39*, 7235; (d) Adrian, L. S.; Christopher, G. T. and Paul, D. L. *Bioorg .Med. Chem. Lett.* **1996**, *6*, 1483; (e) Shingo, M.; Nobuyasu, S.; Eiji, N. and Takashi, T. *Synlett* **2001**, 333.

[6] Toy, P. H. and K. D. Janda, *Acc. Chem. Res.* **2000**, *33*, 46.

[7] (a) Sheng, S. R.; Wang, Q.; Wang, Q. Y.; Guo, L.; Liu, X. L. and Huang, X. *Synlett.* **2006**, 1887; (b) Ribiere, P.; Declerck, V.;

Nedellec, Y.; Yadav, B. N.; Martinez, J. and Lamaty, F. *Tetrahedron* **2006**, *62*, 10456; (c) Yeh, W. B. and Sun, C. M. *J. Comb. Chem.* **2004,** *6*, 279.

[8] (a) Rao, Z.; Peng, H. D.; Yang, G. C. and Chen, Z. X. *Combinatorial Chemistry & High Throughput Screening*. **2006**, *9*, 1743; (b) Yue, G.; Chen, Z. and Yang, G. *J. Heterocyclic Chemistry*. **2006**, *43*, 781; (c) Yue, G.; Wan, Y.; Song, S.; Yang, G. and Chen, Z. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 453; (d) Zhang, H. Q.; Yang, G. C.; Chen, J. N.; Chen, Z. X. *Synthesis*. **2004**, 3055; (e) Chen, Z.; Yue , G. and Yang, G. *Synlett*. **2004**, 1231.

[9] Sauvagnat , B.; Lamaty, F.; Lazaro, R. and Martinez, J. *Tetrahedron Lett*. **2000**, *41*, 6371.

[10] Roger, O. P. S. and Wagner, E. C. *J. Org. Chem*. **1953**, *18*, 1427.

[11] Cortez, R. J.; Rivero, I. A.; Somanathan, R. and Hong , E. *Synth. Comm*. **1991**, *21*, 285.

[12] Ting, K. A.; Ahmet, E. B. and Gerhard V. B., *J. Chem. Soc. Perkin. I*, **1981** 2884.