

## Reports

### Microwave-Assisted and Traceless Synthesis of Imidazoquinoxalinones

Mei-Jung Lin and Chung-Ming Sun\*

Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300, Taiwan

Received April 11, 2006

To discover lead compounds of significant pharmacological activity, it is necessary to screen a large number of compounds within a short period of time. Combinatorial chemistry along with high-throughput screening has been able to generate vast molecular libraries to meet this demand for diversified chemical compounds.<sup>1</sup> Although solid-phase library synthesis offers a practical method with the advantages of fast purification,<sup>2</sup> it is hampered by the heterogeneous conditions and requires a large excess of reagents to drive it to completion. The introduction of soluble polymer supports<sup>3</sup> to combinatorial synthesis has resulted in an alternative method that enables standard solution-based chemistry to be performed with favorable reaction kinetics and product purification similar to solid phase reactions. Furthermore, monitoring progress of reactions on the support is significantly simplified by using conventional analytical methods.<sup>4</sup>

Despite numerous advances in high-throughput synthesis methods, a more practical approach in fast library preparation is emerging. Many polymer-supported reactions require hours or days to complete conversion with conventional heating. Same reactions only take a few minutes to complete with microwave irradiation. Several papers that have applied microwave irradiation in solid- or solution-phase synthesis are now widely reported,<sup>5</sup> and their results demonstrate higher yields and shorter reaction times compared to that of conventional thermal heating. The development of microwave-assisted traceless library synthesis provides rapid access to the targeted compounds without requiring cleavage of the polymer support. To better meet the need of enhancing druglike library synthesis, we report the rapid synthesis of biologically interesting imidazoquinoxalinones by the application of microwave technique and traceless approach.

The heterocyclic systems containing quinoxaline rings were largely investigated and were effective in pharmacological and agrochemical herbicides. For example, pyrazoloquinoxaline showed a relatively high antibacterial activity, wherein the minimum inhibitory concentration (MIC) was 25  $\mu\text{g}/\text{mL}$  against *Bacillus Licheniformis* and *Cellulomonas Sp.*<sup>6–10</sup> The tricyclic fused scaffold incorporating pyrazine

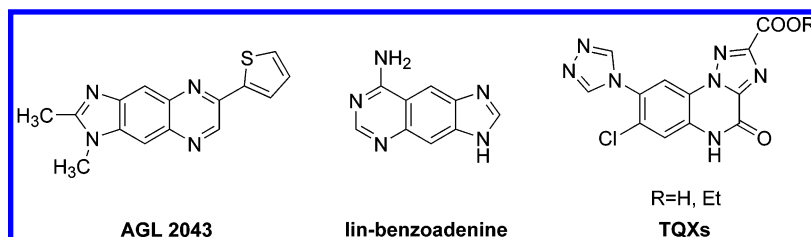
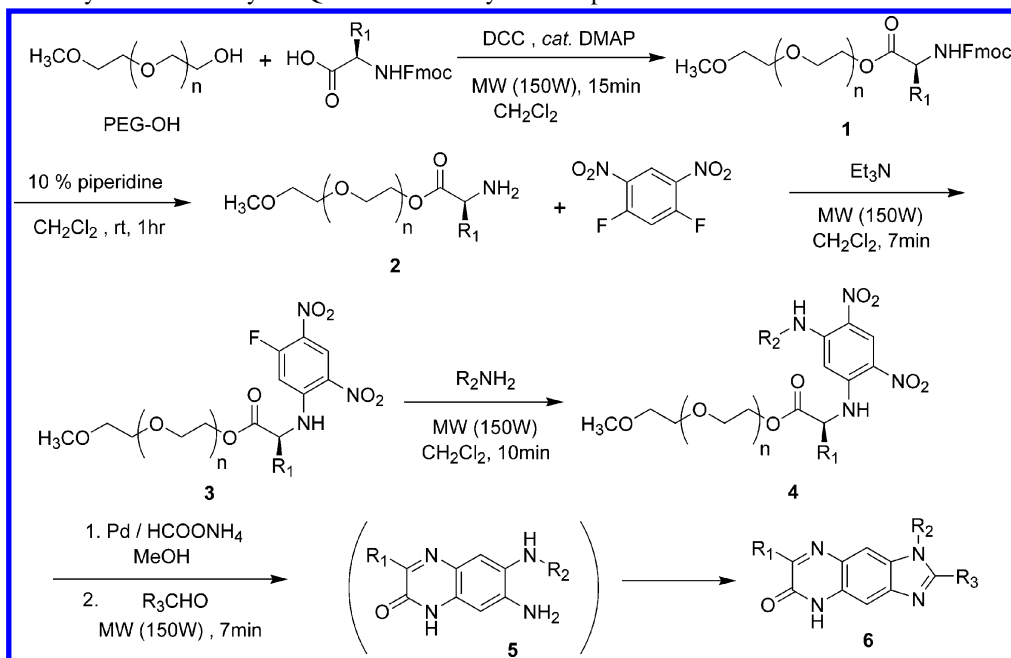
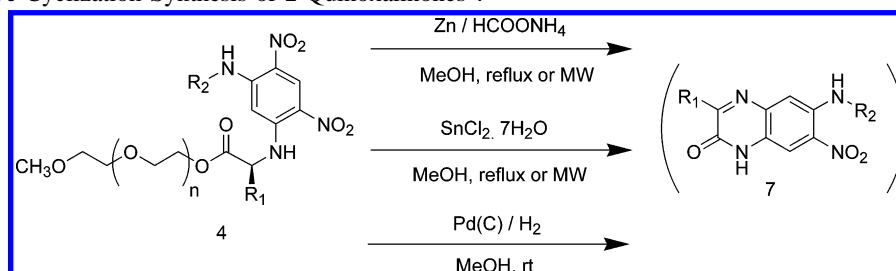
and imidazole with a benzene spacer moiety resulted in compounds with promising biological activation (Figure 1). For example, AGL 2043 blocked PDGFR kinase with inhibitory effects on the related Flt-3 and c-Kit receptors.<sup>11–15</sup>

Lin-benzoadenine has been studied with respect to the exhibition of strong enzyme binding, activation, and action as cofactor in enzymatic reactions.<sup>16</sup> Tricyclic quinoxalinones (TQXs) are reported as selective AMPA receptor antagonists.<sup>17</sup> In continuation of our interest in soluble polymer-supported synthesis of benzimidazoles and quinoxalinones, the present investigation develops an efficient one-pot traceless synthesis of imidazolo[4,5-g]-quinoxalinone on a soluble polymer support under microwave irradiation.

The microwave-assisted multistep synthetic route to the targeted imidazoquinoxalinones is described in Scheme 1. The synthesis starts with esterification of the commercially available Fmoc-protected amino acids with poly(ethylene glycol) (PEG-OH, MW  $\approx$  5000) under microwave conditions for 15 min to obtain the Fmoc-protected amino ester conjugates (**1**). The same coupling reaction was done in 8 h by conventional reflux heating. The regeneration of the free amino group was achieved by treating **1** with 10% piperidine in dichloromethane at room temperature which left the polymer support intact leading to the polymer-bound amines (**2**). The next step in the synthesis is the *ipso*-fluoro displacement reaction with highly electrophilic dinitrofluorobenzene inside the microwave cavity. The reaction proceeds to completion in 7 min resulting in the formation of polymer-bound dinitrofluoro amines (**3**). It should be noted that under harsh microwave heating, no disubstituted species were observed after cleavage of **3**. This could be that immobilized substrate **3** is less reactive than difluoronitrobenzene once one fluoro was first replaced by polymer-bound amino esters **2**. Difluoronitrobenzene has been utilized as a bifunctional cross-linker since it contains two fluoro groups which could be successively substituted by different nucleophiles.<sup>18</sup> The use of this symmetric scaffold for the construction of fused heterocycles by solid-phase synthesis has been published.<sup>18d</sup> However, the acidolysis of acyl-amidoquinoxaline to cleave the polystyrene support is necessary.

The second point of molecular diversity was introduced by another  $\text{S}_{\text{N}}\text{Ar}$  reaction of various alkyl aromatic amines giving rise to the PEG-immobilized dinitro diamines (**4**) under microwave irradiation in 10 min. In contrast, conventional heating for this transformation required 7 h of reflux in EtOH to go to completion. Simultaneous quantitative reduction of the aromatic *m*-dinitro group to the corresponding aniline derivatives was then studied in various conditions. We found that by using either Zn in  $\text{HCOONH}_4$  or tin(II)

\* To whom correspondence should be addressed. Fax: +(886)-3-5736007. E-mail: cmsun@mail.nctu.edu.tw.

**Figure 1.** Pharmacologically active of tricyclic compound.**Scheme 1.** Traceless Synthesis of Tricyclic Quinoxalinones by Multistep Microwave Irradiation**Scheme 2.** Reductive Cyclization Synthesis of 2-Quinoxalinones **7**

chloride dihydrate can deliver traceless synthesis of 2-quinoxalinone analogues **7**, an *o*-nitroaniline intermediate without further reduction of another nitro group (Scheme 2).<sup>19</sup> 3,4-Dihydroquinoxalin-2-one is also a privileged drug-like scaffold which has been shown to have broad biological activity in medicinal chemistry.<sup>20</sup> Microwave-assisted synthesis of chiral quinoxalinone has also been reported.<sup>20f–g</sup> The one-pot reductive bis-*N*-heterocyclization was accomplished in two steps as follows: simultaneous reduction of the two nitro groups was brought about by catalytic transfer hydrogenation using palladium and ammonium formate in methanol by microwave irradiation (10 min, 90 W). The same reduction was completed in 16 h by conventional heating. The nucleophilicity of the in situ generated diamine was used to construct the five-membered ring with aldehydes representing the [4 + 1] approach to benzimidazole. The reduction and cyclization procedure can be operated in a continuous manner toward the tricyclic

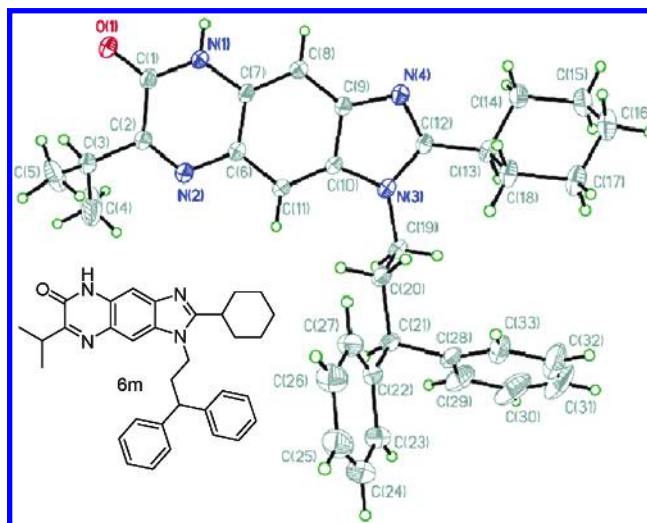
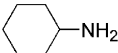
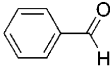
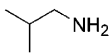
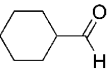
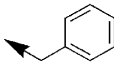
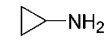
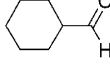
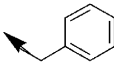
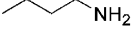
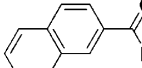
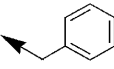
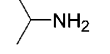
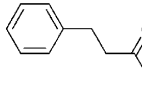
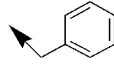
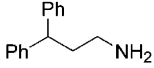
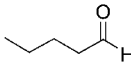
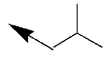
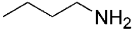
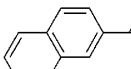
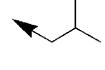
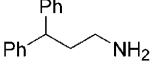
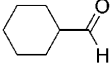
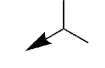
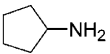
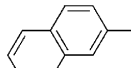
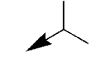

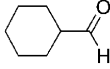
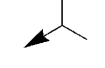
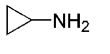
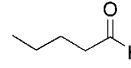
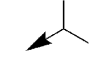
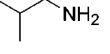
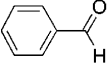
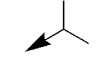
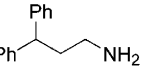
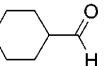
**Figure 2.** ORTEP diagram of **6m** with the crystallographic numbering system.

Table 1. One-Pot Cyclization toward Imidazoquinoxalinones **6**

Entry	R <sub>1</sub>	R <sub>2</sub> NH <sub>2</sub>	R <sub>3</sub> CHO	Mass	Yield <sup>a</sup>
6a	H			344	86%
6b	H			324	95%
6c				398	90%
6d				458	91%
6e				422	85%
6f				526	92%
6g				424	88%
6h				518	94%
6i				422	84%
6j				366	85%
6k				324	92%
6l				360	88%
6m				504	90%

<sup>a</sup> Yields were determined on weight of purified samples.

quinoxalinone imidazoles **6**. This reaction was carried out successfully without further addition of acidic catalysts.<sup>21,22</sup> It should be mentioned that no other oxidants, such as DDQ and oxone, are needed to assist benzimidazole cyclization.<sup>23</sup> Under the harsh microwave conditions employed, this was also accompanied by the cleavage of the polymer support by an intramolecular nucleophilic attack on the polymer attached site and no more cleavage step was required.<sup>24</sup> Simultaneous cyclization with various aldehydes was brought about in 7 min by microwave irradiation, whereas the same ring closure reaction is completed within 7 h under classical refluxing conditions. To this end, insoluble palladium/charcoal was removed first by filtration, and the unwanted polymer support was separated from the desired products by selective precipitation after adding diethyl ether to the

reaction mixtures. In this way, one-pot reductive double-ring closure directly leads to the tricyclic quinoxalinone imidazoles **6** in high yields and purities. Complete intramolecular cleavage of the polymer support was verified by the observation of a downfield shift for the  $\alpha$ -methylene protons of the polymer attachment site from 4.4 to 3.6 ppm. The polymer-free compounds, **6**, were yellow solids which were purified by column chromatography with elution using ethyl acetate/hexane (1:1), and they were isolated in a 84–92% yield (Table 1).<sup>25</sup> Additional support for the unambiguous configuration of the **6m** structure was finally confirmed from the X-ray analysis which indicated it is a 3,4-dihydroquinoxalin-2-one but not a hydroxyl-quinoxaline. The IR spectrum of **6** also showed amide absorption that appears in the range of 1680–1630 cm<sup>-1</sup>.

In conclusion, we first explored a combination of microwave techniques and traceless polymer-supported strategies for the synthesis of tricyclic quinoxalinone imidazoles libraries with three points of diversity. Simultaneous reduction of the two nitro groups leads to the intramolecular cyclizative cleavage of polymer support and N-heterocyclization with aldehydes to the formation of imidazole and the quinoxalinone ring in one pot. The coupling of microwave technology with a liquid-phase traceless synthetic strategy constitutes a novel and attractive avenue for the rapid generation of structurally diverse libraries. The biological activities of synthetic libraries will be reported in due time.

**Acknowledgment.** The authors thank the National Science Council of Taiwan for the financial assistance and the authorities of the National Chiao Tung University for providing the laboratory facilities.

**Supporting Information Available.** Representative experimental procedures, spectral, and other data of compounds **6a–m** and the bond angle and bond length data for **6m**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References and Notes

- (1) (a) Len, G. R.; Nash, H. M.; Jindal, S. *Drug Discovery Today* **2000**, *5*, 145–156. (b) Falb, D.; Jindal, S. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 1367–1374.
- (2) (a) Dolle, R. E. *Mol. Diversity* **1996**, *2*, 223–236. (b) Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235–282. (c) Dolle, R. E. *J. Comb. Chem.* **2000**, *2*, 383–433. (d) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477–517. (e) Dolle, R. E. *J. Comb. Chem.* **2003**, *5*, 693–753.
- (3) (a) Yeh, W. B.; Sun, C. M. *J. Comb. Chem.* **2004**, *6*, 279–282. (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546–554. (c) Sun, C. M. In *Combinatorial Chemistry Methods and Protocols*; Bellavance, L., Ed.; Methods in Molecular Biology Series; The Humana Press Inc.: Totowa, NJ, 2002; Chapter 10, pp 345–371.
- (4) Yeh, W. B.; Lin, M. J.; Lee, M. J.; Sun, C. M. *Mol. Diversity* **2003**, *7*, 185–198.
- (5) For microwave-assisted solid-phase combinatorial synthesis, see: (a) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624–630. (b) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105. (c) Wilson, N. S.; Roth, G. P. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 620–629. (d) Al-Obeidi, F.; Austin, R. E.; Okonya, J. F.; Bond, D. R. S. *Mini-Rev. Med. Chem.* **2003**, *3*, 459–470. (e) Swamy, K. M. K.; Lin, M. J.; Yeh, W. B.; Sun, C. M. *Curr. Med. Chem.* **2003**, *10*, 2403–2424. (f) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
- (6) Kaneko, C.; Katagiri, S. (Asahi Glass Co. Ltd) *Jpn. Kokai Tokkyo Koho* **1988**, *62*, 207, 264.
- (7) Hiramatsu, T.; Azuma, S.; Nakagawa, K.; Ichikawa, Y. (Teijin Ltd.) *Jpn. Kokai Tokkyo Koho* **1988**, *62*, 163, 263.
- (8) (a) Makino, K.; Kim, H. S.; Yoshihisa, K. *J. Heterocycl. Chem.* **1988**, *35*, 321–326. (b) Makino, K.; Kim, H. S.; Yoshihisa, K. *J. Heterocycl. Chem.* **1998**, *35*, 489–497.
- (9) Zhu, Z.; Saluga, S.; Drach, C. J.; Townsend, L. P. *J. Chin. Chem. Soc.* **1988**, *45*, 465–474.
- (10) Mange, A.; Palop, J. A.; Urbasos, I.; Fernandez-Alvarez, E. *J. Heterocycl. Chem.* **1989**, *26*, 1623–1626.
- (11) Levitzki, A.; Gazit, A.; Banai, S.; Golomb, G.; Gertz, D. US Patent 6, 358, 954, 2002.
- (12) Levitzki, A. *Pharmacol. Ther.* **1999**, *82*, 231–239.
- (13) Karck, M.; Meliss, M. R.; Hestermann, M.; Mengel, M.; Pethig, K.; Levitzki, A.; Banai, S.; Golomb, G.; Fishbein, I.; Chorny, M.; Haverich, A. *Transplantation* **2002**, *74*, 1335–1341.
- (14) George, D. *Semin. Oncol.* **2001**, *5*, 27–32.
- (15) Gilliland, D. G.; Griffin, J. D. *Blood* **2002**, *100*, 1532–1542.
- (16) Heinrich, M. C.; Rubin, B. P.; Longley, B. J.; Fletcher, J. A. *Hum. Pathol.* **2002**, *33*, 484–495.
- (17) Catarzi, D.; Colotta, V.; Varano, F.; Cecchi, L.; Filacchioni, G.; Gallii, A.; Costagli, C.; Carla, V. *J. Med. Chem.* **2000**, *43*, 3824–3826.
- (18) (a) Deyev, S. M.; Afanasenko, G. A.; Polyakov, O. L. *Biochim. Biophys. Acta* **1978**, *534*, 358–367. (b) Fitzgerald, T. J.; Carlson, G. M. *J. Biol. Chem.* **1984**, *259*, 3266–3274. (c) Liu, G.; Fan, Y.; Carlson, J. R.; Zhao, Z. G.; Lam, K. S. *J. Comb. Chem.* **2000**, *2*, 467–474. (d) Mazurov, A. *Tetrahedron Lett.* **2000**, *41*, 7–10. (e) Li, L.; Liu, G.; Wang, Z.; Yuan, Y.; Zhang, C.; Tian, H.; Wu, X.; Zhang, J. *J. Comb. Chem.* **2004**, *6*, 811–821. (f) Cumpste, I.; Carlsson, S.; Leffler, H.; Nilsson, U. *J. Org. Biomol. Chem.* **2005**, *3*, 1922–1932. (g) Liu, G.; Zhang, J.; Zhang, L.; Zhang, S.; Wang, Y. *J. Comb. Chem.* **2005**, *7*, 657–664.
- (19) (a) Morita, S.; Kitano, K.; Matsubara, J.; Ohtani, T.; Kawano, Y.; Otsubo, K.; Uchida, M. *Tetrahedron* **1998**, *54*, 4811–4818. (b) Conversion of Nitro Compounds into Other Compounds. In *The Nitro Group in Organic Synthesis*; Ono, N. A., Ed.; John Wiley & Sons Publications: New York, 2001; p 159.
- (20) (a) Perez, C.; Lopez, de C. A.; Bello, J. *Food Chem. Toxicol.* **2002**, *40*, 1463–1467. (b) Quint, C.; Temmel, A. F.; Hummel, T.; Ehrenberger, K. *Acta Otolaryngol.* **2002**, *122*, 877–881. (c) Mensah-Osman, E. J.; Al-Katib, A. M.; Dandashi, M. H.; Mohammad, R. M. *Mol. Cancer Ther.* **2002**, *1*, 1315–1320. (d) Seitz, L. E.; Suling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2002**, *45*, 5604–5606. (e) Burke, J. R.; Pattoli, M. A.; Gregor, K. R.; Brassil, P. J.; MacMaster, J. F.; McIntyre, K. W.; Yang, X.; Iotzova, V. S.; Clarke, W.; Strnad, J.; Qiu, Y.; Zusi, F. C. *J. Biol. Chem.* **2003**, *278*, 1450–1456. (f) Zhang, W.; Tempest, P. *Tetrahedron Lett.* **2004**, *45*, 6757–6760. (g) Sun, C. M.; Tung, C. L. *Tetrahedron Lett.* **2004**, *45*, 1159–1162.
- (21) Jonas, R.; Klockow, M.; Lues, I.; Prücher, H.; Schliep, H. J.; Wurziger, H. *Eur. J. Med. Chem.* **1993**, *28*, 129–140.
- (22) Smith, J. M.; Krachóák, V. *Tetrahedron Lett.* **1999**, *40*, 7633–7636.
- (23) Beaulieu, P. L.; Haché, B.; Moos, E. *Synthesis* **2003**, *11*, 1683–1692.
- (24) All the microwave-assisted polymer-supported reactions described here were performed in a CEM Discover Microwave System at a frequency of 2450 Hz (0–300 W) in open vessel system.
- (25) Analytical data for cleaved compound **6j**. 1-Butyl-2-cyclohexyl-7-isopropyl-1H-imidazo[4,5-g]quinoxalin-6-one. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 12.14 (bs, 1H, NH), 7.75 (s, 1H), 7.67 (s, 1H), 4.16 (t, J = 7.6 Hz, 2H), 3.71–3.58 (m, 1H), 2.87–2.80 (m, 1H), 2.00–1.79 (m, 10H), 1.50–1.29 (m, 4H), 1.38 (d, J = 6.8 Hz, 6H), 1.00 (t, J = 7.3 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 163.5, 162.7, 155.9, 143.6, 132.6, 129.6, 127.4, 108.3, 103.4, 53.4, 43.7, 36.7, 32.1, 31.9, 30.7, 26.3, 25.7, 20.2, 13.7. IR (cm<sup>-1</sup>, neat): 2931, 2839, 1666, 1455, 1402. MS (EI): m/z 366 (M<sup>+</sup>). Exact mass calcd for C<sub>22</sub>H<sub>30</sub>N<sub>4</sub>O: m/z 366.2420. Found 366.2431.

CC060051D