Journal of the Korean Chemical Society
2017, *Vol. 61, No. 5*
Printed in the Republic of Korea
https://doi.org/10.5012/jkcs.2017.61.5.299

Notes

Diversification of Imidazo[1,2-*a*]pyridines under Microwave–Assisted Palladium-Catalyzed Suzuki Reaction

Jin-Hee Lee, Seung Yeong Park, Areum Park, and Eul Kgun Yum*
Department of Chemistry, Chungnam National University, Yusung, Daejon 34134, Korea.
**E-mail: ekyum@cnu.ac.kr*
(Received July 3, 2017; Accepted August 11, 2017)

Key words: Microwave, Palladium, Suzuki reaction, Aryl coupling, Bromoimidazo[1,2-*a*]pyridines

INTRODUCTION

The imidazole-fused six-membered heterocycles are fundamental chemical structures in biological systems.[1] The major interest in ring systems is due to their resemblance to biologically important purines. The imidazo[1,2-*a*]pyridine has recently received increased attention due to its use in natural products and pharmaceuticals.[2] Specifically, arylated imidazo[1,2-*a*]pyridines are used as drugs to treat various diseases (*Fig*. 1).[3] Many recent biological studies of imidazo[1,2-*a*]pyridine derivatives have shown a broad spectrum of activities, such as antibacterial,[4] antiviral,[5] antiprotozoal,[6] respiratory virus fusion inhibitor,[7] and anticancer activities.[8] Based on previous biological studies, minor changes in the chemical structure of imidazo[1,2-*a*]pyridines are responsible for significant changes in biological activities.

Therefore, organic chemists have reported various synthetic strategies for the construction of imidazo[1,2-*a*]pyridines.[9] Although extensive synthetic investigations of imidazo [1,2-*a*]pyridines have been performed,[10] the development of new methods remains desirable for the functionalization of imidazo[1,2-*a*]pyridines under simple and mild reaction conditions. Recently, microwave-mediated organic reactions have attracted considerable attention from organic chemists because microwave heating can accelerate slow thermal reactions with significant energy savings, high chemical yields, and cleaner reactions.[11] Our group explored diversification of heterocyclic moieties, such as indole, azaindole, carbazole, and thiazole under microwave reactions with palladium- or copper-catalyzed cross-coupling reactions.[12] These reactions are powerful synthetic tools to establish diverse heterocyclic moieties. To establish a heterocyclic chemical library for biological studies, we require a convenient and rapid synthetic procedure to obtain diverse arylated imidazo[1,2-*a*]pyridines. In this report, we examined the microwave-assisted palladium-catalyzed Suzuki reaction with various bromoimidazo[1,2-*a*]pyridines, and substituted arylboronic acids to obtain diversified arylated imidazo[1,2-*a*]pyridines.

RESULTS AND DISCUSSION

The 2-substituted imidazo[1,2-*a*]pyridines were prepared by condensation of suitable 2-aminopyridine with appropriate haloacetyl derivatives in ethanol refluxing for 12–24 hours, as described previously.[13] Further bromination of 2-substituted imidazo[1,2-*a*]pyridines with NBS provided the corresponding 3-bromoimidazo[1,2-*a*]pyridines (*Scheme* 1).

Initially, the reaction of 3-bromoimidazo[1,2-*a*]pyridine with phenylboronic acid was selected as a preliminary model to establish standard reaction conditions with microwave heating. The reaction conditions were optimized by varying the palladium species, base, solvent, and temperature. The results are summarized in *Table* 1.

We investigated the effects of different Pd catalysts, bases, and solvents under various reaction temperatures to

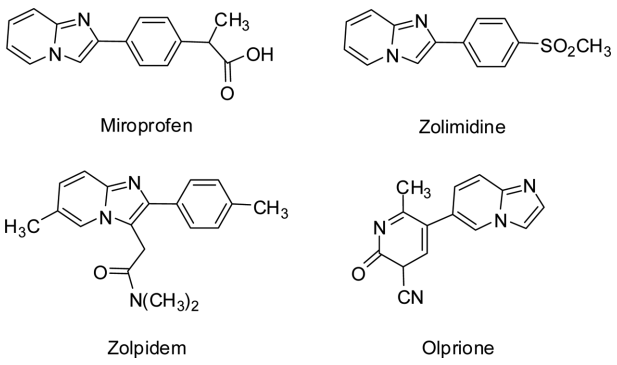
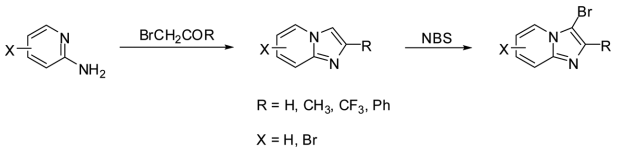


***Figure* 1.** Structure of arylated imidazo[1,2-*a*]pyridines as drugs.



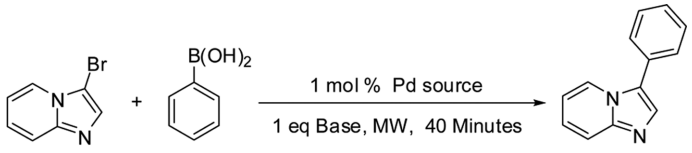
***Scheme* 1.** Synthesis of substituted imidazo[1,2-*a*]pyridine.

examine the reactivity and stability of 3-bromoimidazo[1,2-*a*] pyridine. The reactions showed reasonable yields of desired product with debrominated starting material under 150–170 °C (Entry 1–2), but reactions under 110 °C provided lower yields of desired products with large amounts of unreacted starting halides (Entry 4). The reaction was performed at 130 °C with various alkaline carbonates and provided good yields of desired products (Entries 4-7). The reaction using Cs_2CO_3 as a base provided higher yields than the reaction using Na_2CO_3 or K_2CO_3. The reaction using different ligand substituted palladium species provided the best yields of desired product with $Pd(PPh_3)_4$ (Entries 3 and 7–9). Finally, reactions using different solvents were examined with *N,N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), 1,4-dioxane, and *N,N*-dimethylacetamide (DMA). The reaction using DMF gave higher yields of desired product compared with other selected solvents (Entries 3 and 10–12). The vapor pressure of the reaction mixture in the vial was monitored to maintain 3–5 bar using an online-programmed Biotage microwave reactor at 130 °C. The results showed that optimal conditions for the Suzuki reaction were 1 mol % Pd $(PPh_3)_4$ and 1 equiv. Cs_2CO_3, in DMF at 130 °C. The aryl-aryl coupling reactions with several 3-bromoimidazo[1,2-*a*]pyridine and functional group-substituted phenylboronic acids were performed under established optimal reaction conditions to obtain 3-arylated imidazo[1,2-*a*]pyridine. The results are summarized in *Table* 2.

The reaction using 3-bromoimidazo[1,2-*a*]pyridine (**1a**) with an electron-donating or -withdrawing substituted phenylboronic acid provided reasonable to good yields of desired product (compound **2a**–**2i)**, Based on these results, the electronic effect of phenylboronic acids did not strongly influence product yields. The reactions using 2-phenylimidazo[1,2-*a*]pyridine with the electron-withdrawing substituted phenylboronic acid did not strongly influence yields of the desired product. Other reactions using 3-bromo-2-trifuloromethylimidazo[1,2-*a*]pyridine gave about 15% higher yields than the reaction using 3-bromoimidazo[1,2-*a*]pyridine with the same arylboronic acid (**2j**, **2k**, and **2l**). The reaction using 2-substitutent of 3-bromoimidazo[1,2-*a*]pyridine did not show significant electronic effects with substituted arylboronic acids.

We further investigated the scope of the reaction with different isomeric bromoimidazo[1,2-*a*]pyridines and various

***Table* 1.** Optimization of palladium-catalyzed Suzuki coupling with 3-bromoimidazo[1,2-*a*]pyridines

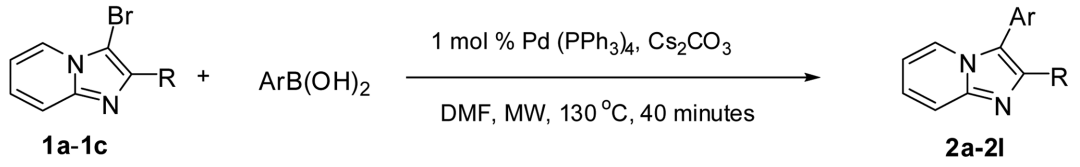


1a **2a**

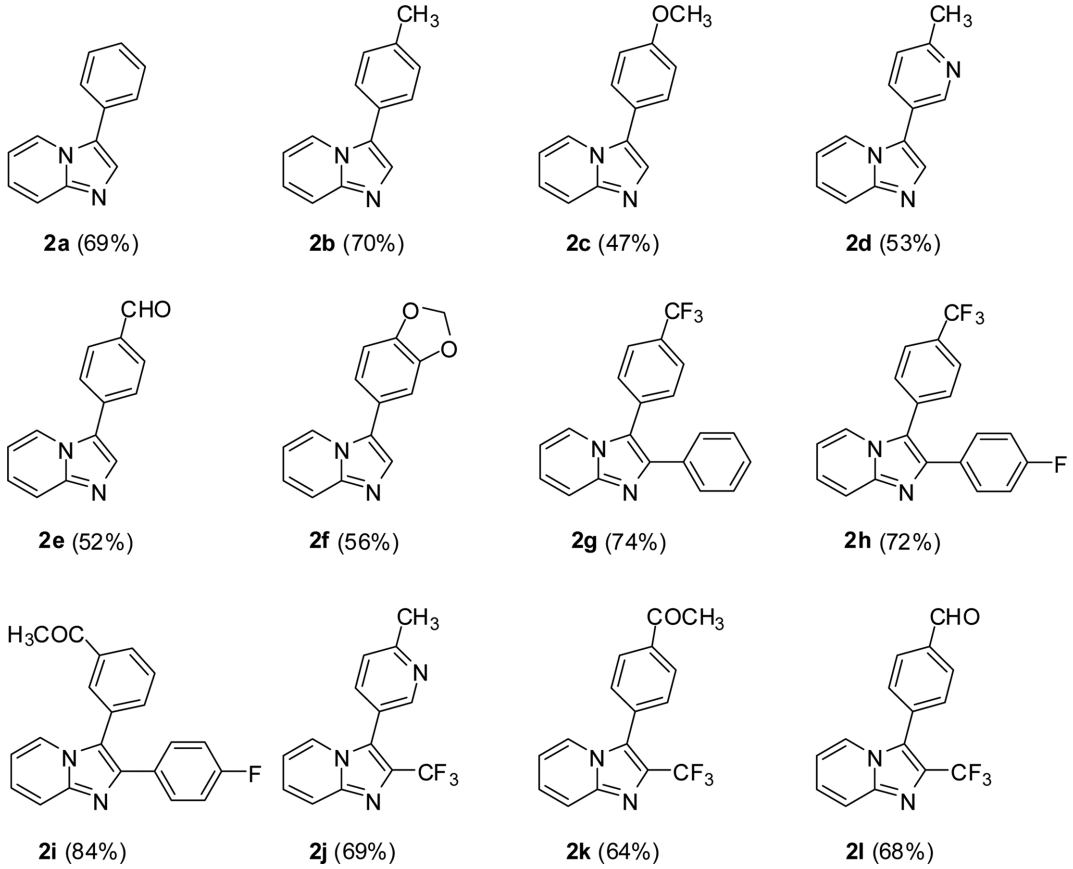
Entry[a]	Pd source	Base	Solvent	Temperature (°C)	Isolated yields (%)
1	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	170	58
2	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	150	63
3[b]	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	130	69 (53) [b]
4	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	110	46
5	$Pd(PPh_3)_4$	Na_2CO_3	DMF	130	37
6	$Pd(PPh_3)_4$	K_2CO_3	DMF	130	49
7	$Pd(OAc)_2$	Cs_2CO_3	DMF	130	37
8	$Pd(dppf)Cl_2$	Cs_2CO_3	DMF	130	30
9	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	DMF	130	44
10	$Pd(PPh_3)_4$	Cs_2CO_3	1,4-dioxane	130	46
11	$Pd(PPh_3)_4$	Cs_2CO_3	NMP	130	52
12	$Pd(PPh_3)_4$	Cs_2CO_3	DMA	130	39

[a]All reacions were conducted at the 1.0 mmol scale in 3 mL of solvent in a Biotage 5 mL vial sealed with a crimp cap. Microwave radiation was supplied with a Biotage Initiator instrument (400 W, 2450 MHz, EXP EU, Biotage).
[b]Thermal heating reaction provided 53% yield of desired product at 150 °C for 12 hours.

***Table* 2.** Synthesis of 3-arylated imidazo[1,2-*a*]pyridines with 3-bromoimidazo[1,2-*a*]pyridines and arylboronic acids



1a-1c **2a-2l**



2a (69%) **2b** (70%) **2c** (47%) **2d** (53%)

2e (52%) **2f** (56%) **2g** (74%) **2h** (72%)

2i (84%) **2j** (69%) **2k** (64%) **2l** (68%)

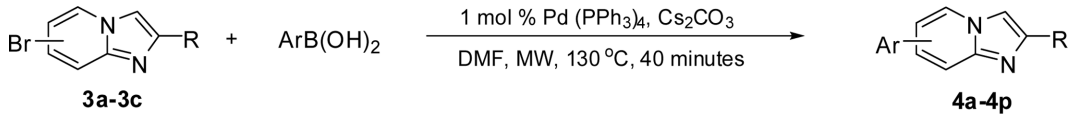
phenyl boronic acids using our established reaction conditions. Reactions using 7-bromoimidazo[1,2-*a*]pyridine with electron-donating or -withdrawing substituted arylboronic acid also gave moderate to good yields of 7- arylimidazo[1,2-*a*]pyridine (compound **4a–4j**). The reactions also showed that the electronic effect of arylboronic acid did not strongly influence product yields.

The reaction using 5- or 6-bromoimidazo[1,2-*a*]pyridine also proceeded under mild reaction temperatures with good yields of desired product (**4k–4p**). The yields of coupling product did not depend on the position of bromoimidazo[1,2-*a*]pyridine. Bromoimidazo[1,2-*a*]pyridine showed a significantly decreased reaction time for the thermal reaction (6–24 h) versus the microwave-assisted reaction (40 min). Specifically, the microwave-assisted palladium-catalyzed carbon-carbon was very useful for establishing a diverse arylated imidazo[1,2-*a*]pyridine library within 1 hour with low % Pd catalyst.

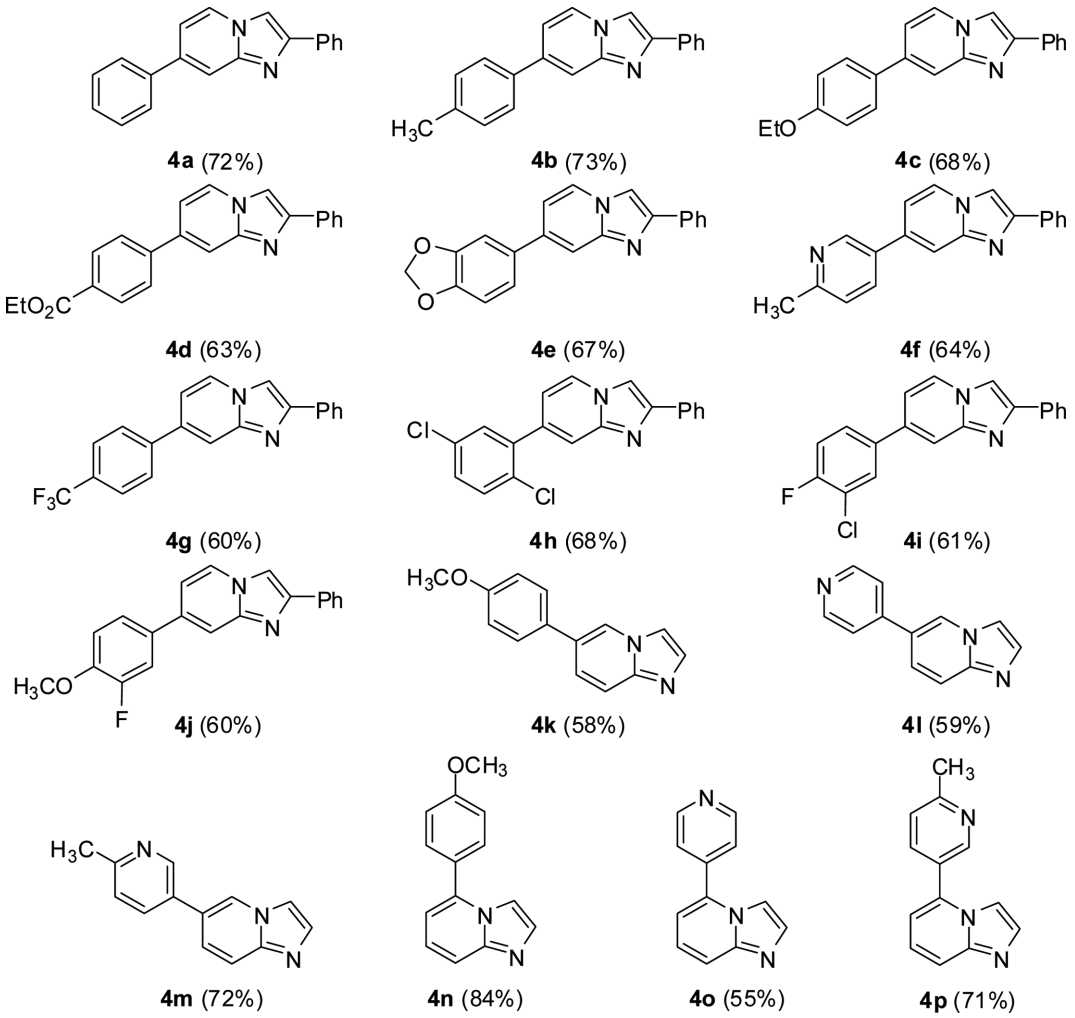
CONCLUSIONS

The microwave assisted palladium-catalyzed Suzuki coupling of 3, 5, 6, and 7- bromoimidazo[1,2-*a*]pyridine with arylboronic acids provided diversified arylimidazo[1,2-*a*] pyridine derivatives with a short reaction time. Although the yields of coupling product varied with arylboronic acid and isomeric bromoimidazo[1,2-*a*]pyridine substituents, the reactions could use various arylboronic acids for diversification. The catalyst system also showed valuable development of green and simple procedures for arylated imidazo

***Table* 3.** Palladium-catalyzed arylation with 5–7-bromoimidazo[1,2-*a*]pyridines



3a-3c **4a-4p**



4a (72%) **4b** (73%) **4c** (68%)

4d (63%) **4e** (67%) **4f** (64%)

4g (60%) **4h** (68%) **4i** (61%)

4j (60%) **4k** (58%) **4l** (59%)

4m (72%) **4n** (84%) **4o** (55%) **4p** (71%)

[1,2-*a*]pyridine preparations, for use in biological studies.

General Procedure for Microwave-assisted Palladium-catalyzed Suzuki coupling

3-Bromoimidazo[1,2-*a*]pyridines (1.0 mmol), Cs_2CO_3 (1.0 mmol), phenylboronic acid (1.2 mmol), $Pd(PPh_3)_4$ (0.01 mmol), and DMF (3 mL) were added to a 5-mL vial. The vial was sealed with a crimp cap and placed in a Biotage initiator microwave cavity. After irradiation at 130 °C for 40 minutes and subsequent cooling, the reaction mixture was diluted with saturated aqueous ammonium chloride. Products were isolated by extraction into ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Products were purified by silica gel column chromatography using a hexane: ethyl acetate: methyl alcohol (4:4:1) eulent. 3-Phenylimidazo [1,2-*a*]pyridine (**2a**) was obtained with 69% yields.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.33 (d, 1H, J = 3.0 Hz, ArH), 7.70 (s, 1H, ArH), 7.67(d, 1H, J = 3.0 Hz, ArH), 7.39–7.56 (m, 5H, ArH), 7.18 (t, 1H, J = 6.0 Hz, ArH), 6.79 (t, 1H, J = 6.0 Hz, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ 132.6, 132.2, 132.0, 129.3, 129.3, 128.6, 128.4, 128.2, 128.0, 124.2, 123.4, 118.3, 112.6.

Acknowledgements. Financial support from Korean Chemical Bank in KRICT is greatly acknowledged.

REFERENCE

1. (a) Katritziky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry I*, Vol. *5*, Pergamon Press, UK, **1984**, p 607 and references therein (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed., WILEY, UK, **2010**, p 373. (c) Couty, F.; Evano, G. *Comprehensive Heterocyclic Chemistry III*, 3th ed. Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Elsevier, Oxford, **2008**, vol. 11, p 409.
2. (a) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem*. **2007**, *7*, 888, and reference therein. (b) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett*. **2012**, *14*, 4580.
3. (a) Swaninston, H. T.; Keating, G. M. *CNS Drugs* **2005**, *19*, 65. (b) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. *J. Med. Chem*. **1965**, *8*, 305. (c) Ueda, T.; Mizushige, K. *Curr. Vasc. Pharmacol.* **2006**, *4*, 1.
4. (a) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170. (b) Revankar, G. R.; Matthews, J. R.; Robins, R. K. *J. Med. Chem.* **1975**, *18*, 1253.
5. (a) Elhakmoui, A.; Gueiffier, A.; Milhavet, J. C.; Blache, Y.; Chapat, J. P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1937. (b) Gueiffier, A.; Lhassani, M.; Elhakmoui, A.; Snoeck, R.; Andrei, G.; Chavignion, O.; Teulade, J. C.; Kerbal, A.; Essassi, M.; Debouzy, J. C.; Witurowo, J. P.; Blache, Y.; Balzarini, J.; DeClercq, E.; Chapat, J. P. *J. Med. Chem.* **1996**, *39*, 2856. (c) Lhassani, M.; Chavignion, O.; Chezal, J. M.; Teulade, J. C.; Chapat, J. P.; Snoeck, R.; Andrei, G.; Balzarini, J.; DeClercq, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271. (d) Hamdouchi, C.; de Blas, J.; del Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem*. **1999**, *42*, 50. (e) Gudmundsson, K. S.; Williams, J. D.; Drach, J. C.; Townsend, L. *J. Med. Chem.* **2003**, *46*, 1449.
6. (a) Scribber, A.; Dennis, R.; Lee, S.; Ouvry, G.; Perrey, D.; Fisher, M.; Wyvratt, M.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thomson, D.; Schmatz, D.; Biftu, T. *European Journal of Medical Chemistry* **2008**, *43*, 1123. (b) Scribber, A.; Dennis, R.; Hong, S. J.; Lee, S.; McIntyre, D.; Perrey, D.; Feng, D.; Fisher, M.; Wyvratt, M.; Leavitt, P.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thomson, D.; Schmatz, D.; Biftu, T. *European Journal of Medical Chemistry* **2008**, *43*, 1334.
7. Feng, S.; Hong, D.; Wang, B; Zheng, X.; Miao, K.; Wang, L.; Yun, H.; Gao, L.; Zhao, S.; Shen, H. C. *ACS Med. Chem. Lett.* **2015**, *6*, 359.
8. (a) Kamal, A.; Reddy, J. S.; Ramaiah, M. J.; Dastagiri, D.; Bharathi, E. V.; Sasar, M. V. P.; Pushpavalli, S. N. C. V. L.; Ray, P.; Pal-Bhadra, M. *Med. Chem. Commum.* **2010**, *1*, 355. (b) Vilchis-Reyes, M. A.; Zentella, A.; Martinez-Urbina, M. A.; Guzman, A.; Vargas, O.; Apan, M. T. R.; Gallegos, J. L. V.; Diaz, E. *European Journal of Medical Chemistry* **2010**, *45*, 379. (c) Vilchis-Reyes, M. A.; Zentella, A.; Martinez-Urbina, M. A.; Guzman, A.; Vargas, O.; Apan, M. T. R.; Gallegos, J. L. V.; Diaz, E. *European Journal of Medical Chemistry* **2010**, *45*, 379. (d) Kim, Y. B.; Kang, C. W.; Ranatunga, S.; Yang, H.; Sebti, S. M.; Del Valle, J. R. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 4650.
9. Reviews: (a) Kazzouli, S. E.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Letters in Organic Chemistry*, **2012**, *9*, 118. (b) Koubachi, J.; Kazzouli, S. E.; Bousmina, M.; Guillaumet, G. *Eur. J. Org. Chem.* **2014**, 5119. (c) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun*. **2015**, *51*, 1555.
10. (a) Cao, H.; Liu, X.; Liao, J.; Huang, J.; Qiu, H.; Chen, Q.; Chen, Y. *J. Org. Chem.* **2014**, *79*, 11209. (b) Yu, J.; Jin, Y.; Zhang, H.; Yang, X.; Fu, H. *Chem. Eur. J.* **2013**, *19*, 16804. (c) Wang, S.; Liu, W.; Cen, J.; Huang, J.; Zhan, H. *Tetrahedron Lett*. **2014**, *55*, 1589. (d) Masurier, N.; Aruta, R.; Gaumet, V.; Denoyelle, S.; Moreau, E.; Lisowski, V.; Martinez, J.; Maillard, L. T. *J. Org. Chem.* **2012**, *77*, 3679. (e) Tachikawa, Y.; Nagasawa, Y.; Furuhashi, S.; Cui, L.; Yamaguchi, E.; Tada, N.; Miura, T.; Itoh, A. *RSV Adv.* **2015**, *5*, 5951. (f) Dimauro, E. F.; Kennedy, J. M. *J. Org. Chem*. **2007**, *72*, 1013. (g) Crozet, M. D.; Castera-Ducros, C.; Vanelle, P. *Tetraheron Lett* 2**006**, *47*, 7061. (h) Koubachi, J.; Kazzoli, S. E.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *J. Org. Chem.* **2007**, *72*, 7650.
11. (a) Larhed, M. *Microwaves in Organic Synthesis*, Second ed.,Wiley-VCH, Velog GmbH & Co. KGaA, Weinheim, **2006**. (b) Kappe, C. O.; Dallinger, D.; Murphree, S. S. *Practical, Microwave Synthesis for Organic Chemists*, Wiley-VCH, Velog GmbH& Co. KGaA, Weinheim, **2009**. (c) Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127. (d) Gawande, M. B.; Shelke, S. N.; Zboril, R.; Verma, R. S. *Acc. Chem. Res.* **2014**, *47*, 1338.
12. (a) Kwon, J. K.; Cho, J. H.; Ryu, Y. S.; Oh, S. H.; Yum, E. K. *Tetrahedron* **2011**, *67*, 4820. (b) Kim, S. K.; Kim, J.-H.; Park, Y. C.; Kim, J. W.; Yum, E. K. *Tetrahedron* **2013**, *69*, (c) Suh, J. H.; Kang, H. S.; Kim, J. E.; Yum, E. K. *Bull. Korean Chem. Soc.* **2012**, *33*, 2067. (d) Kwon, J. K.; Lee, J. H.; Kim, T. S.; Yum, E. K. *Bull. Korean Chem. Soc.* **2016**, *37*, 1927.
13. Cao, H.; Zhan, H.; Lin, Y.; Lin, X.; Du, Z.; Jiang, H. *Org Lett*. **2012**, *14*, 1688.