ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

One-Pot Synthesis of Benzo[4,5]imidazo[1,2-*a*]quinazoline Derivatives via Facile Transition-Metal-Free Tandem Process

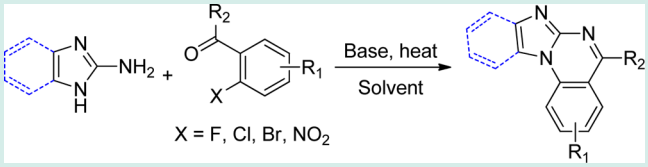
Shuai Fang,[†] Xiaoyi Niu,[†] Bingchuan Yang,[†] Yanqiu Li,[†] Xiaomeng Si,[†] Lei Feng,[†] and Chen Ma*[,†,‡]

[†]Key Laboratory of Special Functional Aggregated Materials, Ministry of Education, School of Chemistry and Chemical Engineering, Shandong University, Jinan, 250100, P. R. China

[‡]State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, P. R. China

Supporting Information

ABSTRACT: A one-pot transition metal-free method for synthesizing benzo[4,5]imidazo[1,2-*a*]quinazoline and imidazo-[1,2-*a*]quinazoline derivatives has been developed. The approach is widely applicable to 2-fluoro-, 2-chloro-, 2-bromo- and 2-nitro-substituted aryl aldehyde and ketone substrates. The fluorescence properties of target compounds were studied.



KEYWORDS: *one-pot synthesis, transition metal-free, benzo[4,5]imidazo[1,2-a]quinazoline derivatives, fluorescence property*

INTRODUCTION

Heterocyclic compounds containing nitrogen-atoms have been broadly applied in pharmaceuticals, and designing novel heterocyclic motifs has become an increasingly urgent mission for chemists.[1] Recently, attention has been paid to benzo[4,5]-imidazo[1,2-*a*]pyrimidine derivatives because of their biological activities (Figure 1). For instance, compound **A** exhibits anti-

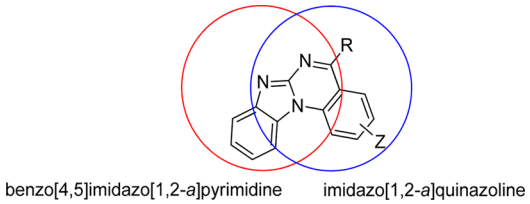


Figure 1. Structure of benzo[4,5]imidazo[1,2-*a*]quinazoline.

inflammatory activity against TNF-α and IL-6,[2] compound **B** has anticancer activity,[3] compound **C** (**T808**) can work as a specific PET tracer for imaging of Tau Pathologies,[4] and compound **D** shows anticancer and analgesic/anti-inflammatory activities.[5] Moreover, benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives also behave as antimicrobial agents.[6] In addition, imidazo[1,2-*a*]-quinazoline also has some effective biological activities. Compound **E** is the inhibitor of apoptosis,[7] and it acts as potent farnesyl protein transferase inhibitor (Figure 2).[8]

We expect that benzo[4,5]imidazo[1,2-*a*]quinazoline derivatives, the combined skeleton of benzo[4,5]imidazo[1,2-*a*]pyrimidine and imidazo[1,2-*a*]quinazoline (Figure 1), might exert certain biological activities. Therefore, it is meaningful to explore a variety of benzo[4,5]imidazo[1,2-*a*]quinazoline scaffolds.

The traditional way to obtain benzo[4,5]imidazo[1,2-*a*]-quinazoline derivatives generally requires a multistep synthesis and harsh conditions. Marini and co-workers utilized 1*H*-benzo-[*d*]imidazol-2-amine and 2-bromobenzoic acid as reactants.

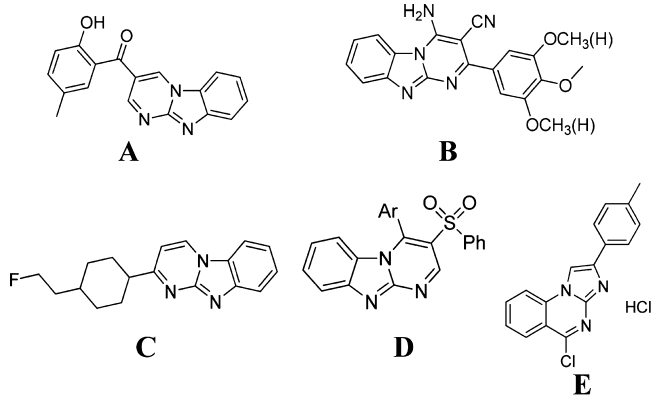


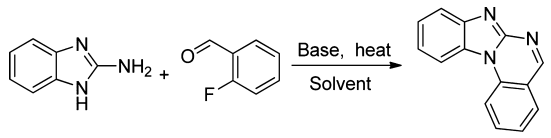
Figure 2. Some biologically important compounds.

Ultimately, target compounds were obtained through a three-step process via Ullman reaction.[9] Pozharskii used 1,8-bis(dimethylamino)-2-naphthaldehyde and 2-aminobenzimidazole as the starting material to gain the desirable compounds, but yields were less than satisfactory.[10]

Notably, the previous literature methods to obtain these heterocyclic compounds were rare and were not adequate in meeting the demands to research structure−activity relationships. Coincidentally, we engaged in constructing these heterocyclic scaffolds[11] and created a novel and efficient one-pot approach to assemble benzo[4,5]imidazo[1,2-*a*]quinazoline derivatives through an addition−elimination/S_NAr process. 1*H*-Benzo[*d*]-imidazol-2-amine and 2-fluoro-, 2-chloro-, 2-bromo-, and 2-nitro-substituted aryl aldehydes and ketones were used as substrates in this process.

Received: January 5, 2014
Revised: May 19, 2014
Published: June 11, 2014

Table 1. Optimization of Reaction Conditions[a]

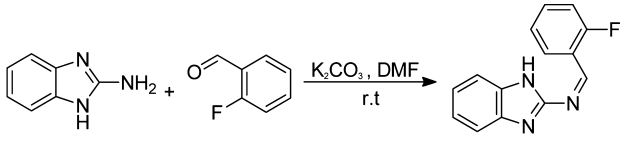


1 2a 3a

entry	solvent	base	T (°C)	time (h)	yield (%)[b]
1	DMF	Cs_2CO_3	120	2	75
2	DMF	NaOH	120	2	79
3	DMF	K_2CO_3	120	2	76
4	DMF	Cs_2CO_3	135	2	93
5	DMF	NaOH	135	2	58
6	**DMF**	**K_2CO_3**	**135**	**2**	**97**
7	DMF	K_2CO_3	135	2	93[c]
8	DMF	K_2CO_3	135	1	55
9	DMF	Cs_2CO_3	135	1	76
10	NMP	Cs_2CO_3	135	2	86
11	Dioxane	K_2CO_3	110	2	Trace
12	DMSO	Cs_2CO_3	135	2	68

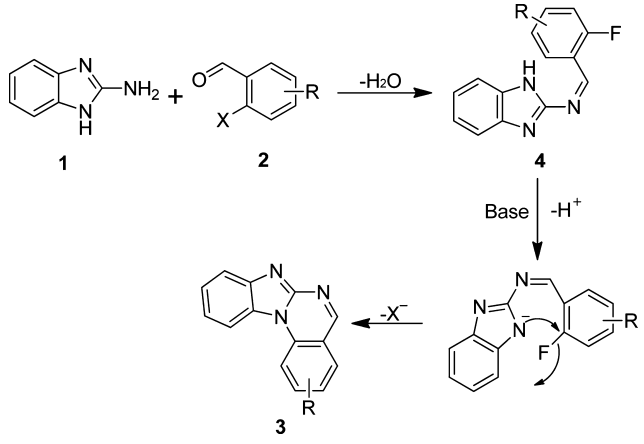
[a]Reaction conditions: 2-aminobenzimidazole **1a** (1.0 equiv), 2-fluorobenzaldehyde **2a** (1.2 equiv), and base (3.0 equiv) under a nitrogen atmosphere. [b]Isolated yields. [c]Reaction with 4 Å molecular series.

Scheme 1. Reaction of 1*H*-Benzo[*d*]imidazol-2-amine and 2-Fluorobenzaldehyde



1 2a 4a

Scheme 2. Plausible Mechanism



1 2 4 3

RESULTS AND DISCUSSION

Initially, we optimized the reaction conditions with 1*H*-benzo[*d*]imidazol-2-amine **1** and 2-fluorobenzaldehyde **2a**. As shown in Table 1, K_2CO_3 in DMF provided the best condition for this transformation (entry 6). Reaction temperature played a key role in the reaction, with the yield being excellent at 135 °C. Moreover, Cs_2CO_3 was equally efficient as K_2CO_3 (entry 1) and a stronger base like NaOH did not favor the reaction (entry 5). In entry 7, the effect of 4 Å molecular sieves was inconspicuous in this reaction system. Solvents were screened as well: NMP and DMSO generated moderate yields, but the reaction in 1,4-dioxane failed to form the product (entries 10−12).

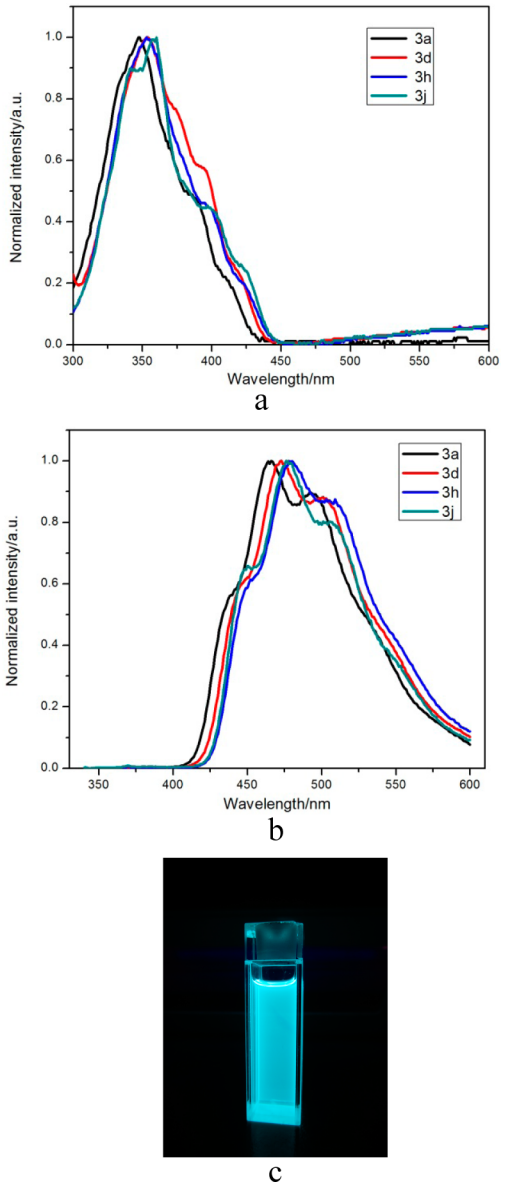


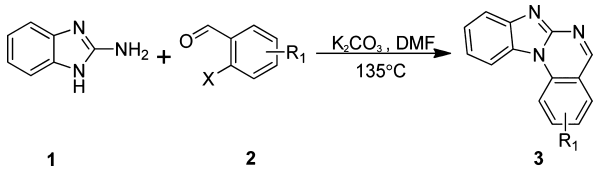
Figure 3. (a) Absorption spectra of **3a**, **3d**, **3h**, and **3j** in DCM. (b) Fluorescence spectra of **3a**, **3d**, **3h**, and **3j** in DCM. (c) Solution luminescence of **3a** in DCM (upon irradiation at 365 nm).

To verify the generality of this reaction, a variety of electron deficient 2-halo- and 2-nitro-substituted aryl aldehydes were tested and found to work efficiently (Table 2, entries 1−4). Particularly, 2-bromobenzaldehyde derivatives coupled efficiently in the absence of a transition metal (entry 3).[12] Interestingly, an excellent yield resulted from the reaction of 1*H*-benzo[*d*]-imidazol-amine **1** and 2-nitrobenzaldehyde **2d** (entry 4). The nitro group has rarely been utilized as a leaving group.[13] The yield from compounds with an electron-donating group was better than those with an electron-withdrawing group (for example, entries 7 and 8). Except for 2-fluoro-5-nitrobenzaldehyde **2m** (entry 13), all the compounds afforded excellent yields.

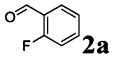
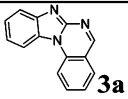
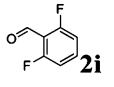
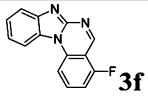
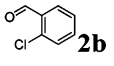
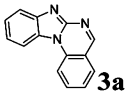
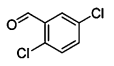
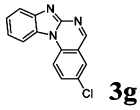
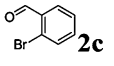
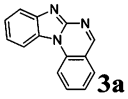
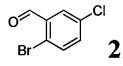
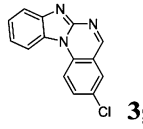
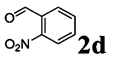
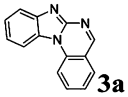
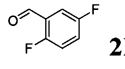
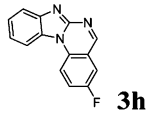
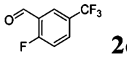
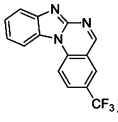
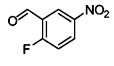
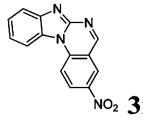
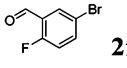
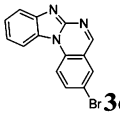
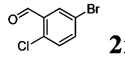
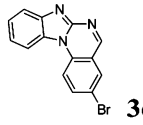
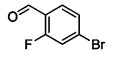
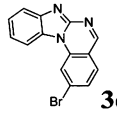
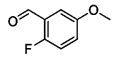
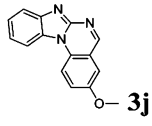
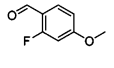
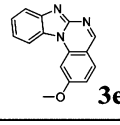
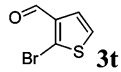
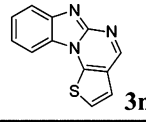
To extend the reaction scope, aryl ketone derivatives were tested (Table 3). Although the reaction between aryl ketone derivatives and arylamines generally demand harsh conditions,[14] reactions worked well for both alkyl aryl ketones (entries 1−3) and diaryl ketones (entry 4). Steric hindrance had no effect on the yield (entry 4).

dx.doi.org/10.1021/co500001u | ACS Comb. Sci. 2014, 16, 328−332

Table 2. Reaction of 1*H*-Benzo[*d*]imidazol-2-amine with 2-Substituted Aryl Aldehydes[a]



1 2 3

Entry	Substrate	Product	Yield/%[b]	Entry	Substrate	Product	Yield/%[b]
1	 **2a**	 **3a**	97	9	 **2i**	 **3f**	92
2	 **2b**	 **3a**	63[c]	10	 **2j**	 **3g**	63[c]
3	 **2c**	 **3a**	70[c]	11	 **2k**	 **3g**	59[c]
4	 **2d**	 **3a**	90	12	 **2l**	 **3h**	80
5	 **2e**	 **3b**	68	13	 **2m**	 **3i**	Trace
6	 **2f**	 **3c**	71	14	 **2n**	 **3c**	65[c]
7	 **2g**	 **3d**	76	15	 **2o**	 **3j**	96
8	 **2h**	 **3e**	91	16	 **3t**	 **3n**	Trace

[a]Reaction conditions: 2-aminobenzimidazole **1** (1.0 equiv), **2** (1.2 equiv) and K_2CO_3 (3.0 equiv) under a nitrogen atmosphere. [b]Isolated yields. [c]Reaction condition: Cs_2CO_3, DMF, 145 °C, 2h.

The reaction between 2-aminoimidazole sulfate and 2-substituted aryl aldehydes was also explored and target products were obtained with moderate yields (Table 4). As previously noted, 2-fluorobenzaldehyde with an electron-donating group achieved a better yield than that with an electron-withdrawing group (entries 5 and 6). Overall, 2-aminoimidazole sulfate **5** (Table 4) was not as efficient as 1*H*-benzo[*d*]imidazol-amine **1** (Table 2 and 3).

To exam the mechanism of these cascade reactions, 1*H*-benzo[*d*]imidazol-2-amine **1** and 2-fluorobenzaldehyde **2a** were reacted as substrates under optimized condition but at room temperature (Scheme 1). Not surprisingly, intermediate **4a** was detected by high resolution mass spectrum (HRMS) after 30 min. Indeed, Schiff base was produced in the first step of this cascade process. From this intermediate, a plausible mechanism is proposed (Scheme 2), wherein intramolecular nucleophilic aromatic substitution reaction (S_NAr) delivers **3**.

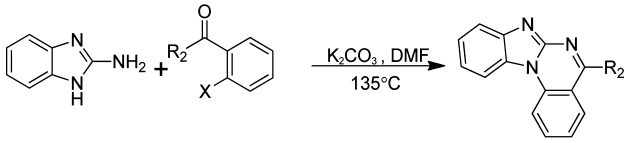
The UV−vis absorption and emission spectra of **3a**, **3d**, **3h**, and **3j** in highly dilute solution were collected (Figure 3). The longest absorption of these products was at 350 nm and the longest emission was at 475 nm. Solution luminescence of **3a** upon irradiation at 365 nm was displayed. The fluorescence efficiency of **3d** is 0.95 in DCM, compared to the quinine sulfate dehydrate.

CONCLUSION

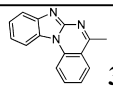
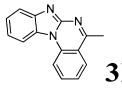
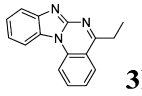
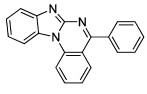
We have developed an efficient method to synthesize a variety of benzo[4,5]imidazo[1,2-*a*]quinazoline and imidazo[1,2-*a*]-quinazoline derivatives via a transition metal-free cascade process. A wide range of 2-fluoro-, 2-chloro-, 2-bromo- and

dx.doi.org/10.1021/co500001u | ACS Comb. Sci. 2014, 16, 328−332

Table 3. Reaction of 1*H*-benzo[*d*]imidazol-2-amine with 2- substituted aryl ketones[a]



1 2 3

Entry	Substrate	Product	Yield/%[b]
1	 **2p**	 **3k**	84
2	 **2q**	 **3k**	56[c]
3	 **2r**	 **3l**	78
4	 **2s**	 **3m**	78

[a]Reaction conditions: 2-aminobenzimidazole **1** (1.0 equiv), **2** (1.2 equiv), and K_2CO_3 (3.0 equiv) under a nitrogen atmosphere. [b]Isolated yields. [c]Reaction condition: Cs_2CO_3, DMF, 145 °C, and 2 h.

2-nitro-substituted aryl aldehyde and ketone substrates performed well in this process. In addition, we tested the fluorescence properties of these compounds. Further pharmaceuticals and materials studies are in process.

EXPERIMENTAL PROCEDURES

General Experimental Procedure for 3a. A mixture of 1*H*-benzo[*d*]imidazol-2-amine **1** (1.0 mmol), 2-fluorobenzaldehyde **2a** (1.2 mmol), and K_2CO_3 (3 mmol) in DMF (5 mL) was stirred at 135 °C under a nitrogen atmosphere. TLC was employed to monitor the end of the reaction. After the mixture was cooled, water was added. The solution was extracted with ethyl acetate (20 mL × 3). The combined organic phase was dried with $MgSO_4$, and the solvent was removed in vacuo to obtain the residue. The residue was purified by column chromatography on silica gel to afford **3a**.

ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures, copies of HRMS, ^1H NMR, and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

AUTHOR INFORMATION

Corresponding Author

*E-mail: chenma@sdu.edu.cn.

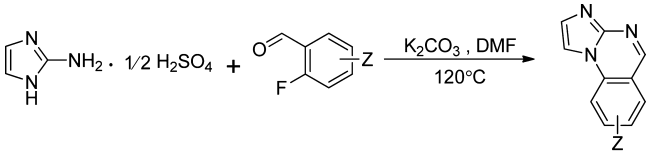
Notes

The authors declare no competing financial interest.

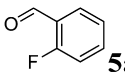
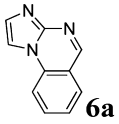
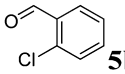
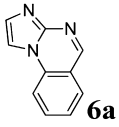
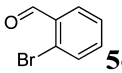
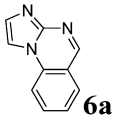
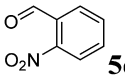
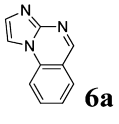
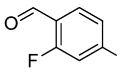
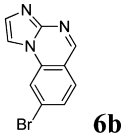
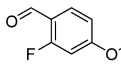
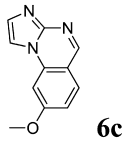
ACKNOWLEDGMENTS

We are grateful to the National Science Foundation of China (No. 21172131) and State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College (No. GTZK201405) for financial support of this research.

Table 4. Reaction of 2-Aminoimidazole Sulfate with 2-Substituted Aryl Aldehydes[a]



5 2 6

Entry	Substrate	Product	Yield/%[b]
1	 **5a**	 **6a**	70
2	 **5b**	 **6a**	45[c]
3	 **5c**	 **6a**	52[c]
4	 **5d**	 **6a**	69
5	 **5e**	 **6b**	60
6	 **5f**	 **6c**	67

[a]Reaction conditions: 2-aminoimidazole sulfate **5** (1.0 equiv), **2** (1.2 equiv), and K_2CO_3 (4.0 equiv) under a nitrogen atmosphere. [b]Isolated yields. [c]Reaction condition: Cs_2CO_3, DMF, 135 °C, 2 h.

REFERENCES

(1) (a) Tsvelikhovsky, D.; Buchwald, S. L. Concise palladium-catalyzed synthesis of dibenzodiazepines and structural analogues. *J. Am. Chem. Soc.* **2011**, *133*, 14228−14231. (b) Kato, J.; Ito, Y.; Ijuin, R.; Aoyama, H.; Yokomatsu, T. Novel strategy for synthesis of substituted benzimidazo[1,2-*a*]quinolines. *Org. Lett.* **2013**, *15*, 3794−3797.

(2) Bharate, S. B.; Mahajan, T. R.; Gole, Y. R.; Nambiar, M.; Matan, T. T.; Kulkarni-Almeida, A.; Balachandran, S.; Junjappa, H.; Balakrishnan, A.; Vishwakarma, R. A. Synthesis and evaluation of pyrazolo[3,4-*b*]pyridines and its structural analogues as TNF-α and IL-6 inhibitors. *Bioorg. Med. Chem.* **2008**, *16*, 7167−7176.

(3) El-Shekeil, A.; Obeid, A. O.; Al-Aghbari, S. Anticancer activity studies of some cyclic benzimidazole derivatives. *Eur. J. Chem.* **2012**, *3*, 356−358.

(4) Zhang, W.; Arteaga, J.; Cashion, D. K.; Chen, G.; Gangadharmath, U.; Gomez, L. F.; Kasi, D.; Lam, C.; Liang, Q.; Liu,

C.; Mocharla, V. P.; Mu, F.; Sinha, A.; Szardenings, A. K.; Wang, E.; Walsh, J. C.; Xia, C.; Yu, C.; Zhao, T.; Kolb, H. C. A highly selective and specific PET tracer for imaging of tau pathologies. *J. Alzheimers Dis.* **2012**, *31*, 601−612.

(5) (a) Shaaban, M. R.; Saleh, T. S.; Mayhoub, A. S.; Farag, A. M. Single step synthesis of new fused pyrimidine derivatives and their evaluation as potent Aurora-A kinase inhibitors. *Eur. J. Med. Chem.* **2011**, *46*, 3690−3695. (b) Shaaban, M. R.; Saleh, T. S.; Mayhoub, A. S.; Mansour, A.; Farag, A. M. Synthesis and analgesic/anti-inflammatory evaluation of fused heterocyclic ring systems incorporating phenylsulfonyl moiety. *Bioorg. Med. Chem.* **2008**, *16*, 6344−6352.

(6) (a) Abdelhamid, A. O.; Abdelall, E. K. A.; Abdel-Riheem, N. A.; Ahmed, S. A. Synthesis and antimicrobial activity of some new 5-arylazothiazole, pyrazolo[1,5-*a*]pyrimidine, [1,2,4]triazolo[4,3-*a*]-pyrimidine, and pyrimido[1,2-*a*]benzimidazole derivatives containing the thiazole moiety. *Phosphorus Sulfur Silicon Relat. Elem.* **2010**, *185*, 709−718. (b) Farghaly, T.; Abdallah, M.; Aziz, M. Synthesis and antimicrobial activity of some new 1,3,4-thiadiazole derivatives. *Molecules* **2012**, *17*, 14625−14636.

(7) Barchéchath, S. D.; Tawatao, R. I.; Corr, M.; Carson, D. A.; Cottam, H. B. Inhibitors of apoptosis in lymphocytes: Synthesis and biological evaluation of compounds related to pifithrin-α. *J. Med. Chem.* **2005**, *48*, 6409−6422.

(8) Angibaud, P.; Bourdrez, X.; End, D. W.; Freyne, E.; Janicot, M.; Lezouret, P.; Ligny, Y.; Mannens, G.; Damsch, S.; Mevellec, L.; Meyer, C.; Muller, P.; Pilatte, I.; Poncelet, V.; Roux, B.; Smets, G.; Van Dun, J.; Van Remoortere, P.; Venet, M.; Wouters, W. Substituted azoloquinolines and -quinazolines as new potent farnesyl protein transferase inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4365−4369.

(9) Da Settimo, A.; Primofiore, G.; Da Settimo, F.; Pardi, G.; Simorini, F.; Marini, A. M. An approach to novel fused triazole or tetrazole derivatives starting from benzimidazo[1,2-*a*]quinazoline-5(7*H*)-one and 5,7-dihydro-5-oxopyrido[3′,2′:5,6]pyrimido[1,2-*a*]-benzimidazole. *J. Heterocycl. Chem.* **2002**, *39*, 1007−1011.

(10) Povalyakhina, M. A.; Antonov, A. S.; Dyablo, O. V.; Ozeryanskii, V. A.; Pozharskii, A. F. H-bond-assisted intramolecular nucleophilic displacement of the 1-NMe_2 group in 1,8-bis(dimethylamino)-naphthalenes as a route to multinuclear heterocyclic compounds and strained naphthalene derivatives. *J. Org. Chem.* **2011**, *76*, 7157−7166.

(11) (a) Zhao, Y.; Dai, Q.; Chen, Z.; Zhang, Q.; Bai, Y.; Ma, C. One pot regioselective synthesis of a small library of dibenzo[*b*,*f*][1,4]-thiazepin-11(10*H*)-ones via smiles rearrangement. *ACS Comb. Sci.* **2013**, *15*, 130−134. (b) Huang, A.; Chen, Y.; Zhou, Y.; Guo, W.; Wu, X.; Ma, C. An efficient one-pot synthesis of benzo[4,5]imidazo[1,2-*a*]quinoxalines via copper-catalyzed process. *Org. Lett.* **2013**, *15*, 5480−5483. (c) Niu, X.; Yang, B.; Li, Y.; Fang, S.; Huang, Z.; Xie, C.; Ma, C. A transition metal-free tandem process to pyridazinopyrido-[3,2-*f*][1,4]thiazepine-diones via smiles rearrangement. *Org. Biomol. Chem.* **2013**, *11*, 4102. (d) Zhao, Y.; Wu, Y.; Jia, J.; Zhang, D.; Ma, C. One-pot synthesis of benzo[1,4]thiazin-3(4*H*)-ones and a theoretical study of the S−N type smiles rearrangement mechanism. *J. Org. Chem.* **2012**, *77*, 8501−8506.

(12) (a) Monnier, F.; Taillefer, M. Catalytic C−C, C−N, and C−O Ullmann-type coupling reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954−6971. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl−aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.* **2002**, *102*, 1359−1470.

(13) (a) Zhang, X.; Jia, J.; Ma, C. A one-pot regioselective synthesis of benzo[*d*]imidazo[2,1-*b*]thiazoles. *Org. Biomol. Chem.* **2012**, *10*, 7944. (b) Li, Y.; Zhan, C.; Cao, X.; Yang, B.; Ma, C. A one-pot transition-metal-free tandem process to 1,4-benzodiazepine scaffolds. *Synthesis* **2012**, *45*, 111−117.

(14) (a) Barluenga, J.; Jiménez-Aquino, A. n.; Aznar, F.; Valdés, C. Modular synthesis of indoles from imines and *o*-dihaloarenes or *o*-chlorosulfonates by a Pd-catalyzed cascade process. *J. Am. Chem. Soc.* **2009**, *131*, 4031−4041. (b) Mrsić, N.; Minnaard, A. J.; Feringa, B. L.; Vries, J. G. d. Iridium/monodentate phosphoramidite catalyzed asymmetric hydrogenation of N-aryl imines. *J. Am. Chem. Soc.* **2009**, *131*, 8358−8359.