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Metal-Free, Acid-Promoted Synthesis of Imidazole Derivatives via a Multicomponent Reaction

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ABSTRACT

An expedient and metal-free synthetic route has been developed for the construction of tri- and tetrasubstituted imidazole derivatives *via* acid promoted multicomponent reaction methodology. The reaction proceeded smoothly with a range of functionalities to produce the imidazole scaffolds in good to excellent yields.

Diversified imidazole scaffolds are a vital class of heterocycles because of their abundance in natural products[1] and broad use in the field of medicinal chemistry.[2] In particular, they are well-known for their anticancer,[3] antifungal,[4] and antibacterial activities.[5] On the other hand, highly substituted imidazoles derivatives possess good photophysical properties, which result in their potential in material chemistry application such as organic electroluminescent devices (OLED).[6] In addition, imidazole derivatives were utilized as ligands in the metal catalyzed reaction[7] and also as fluorescent probes.[8] Based on the above facts, a variety of synthetic routes have been devised for the synthesis of imidazole analogues.[9]

In general, 2,4,5-trisubstituted imidazoles were synthesized by the reaction of 1,2-diketone or keto-monoxime or

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(1) (a) Cui, B.; Zheng, B. L.; He, K.; Zheng, Q. Y. *J. Nat. Prod.* **2003**, *66*, 1101. (b) Tsukamoto, S.; Kawabata, T.; Kato, H.; Ohta, T.; Rotinsulu, H.; Mangindaan, R. E. P.; Van Soest, R. W. M.; Ukai, K.; Kobayashi, H.; Namikoshi, M. *J. Nat. Prod.* **2007**, *70*, 1658.

(2) (a) Riduan, S. N.; Zhang, Y. *Chem. Soc. Rev.* **2013**, *42*, 9055. (b) Bhatnagar, A.; Sharma, P. K.; Kumar, N. *Int. J. PharmTech Res.* **2011**, *3*, 268.

(3) (a) Baroniya, S.; Anwer, Z.; Sharma, P. K.; Dudhe, R.; Kumar, N. *Der Pharmacia Sinica* **2010**, *1*, 172. (b) Perchellet, E. M.; Perchellet, J.-P.; Baures, P. W. *J. Med. Chem.* **2005**, *48*, 5955.

(4) (a) Rani, N.; Sharma, A.; Gupta, G. K.; Singh, R. *Mini Rev. Med. Chem.* **2013**, *11*, 1626. (b) Santo, R. D.; Tafi, A.; Costi, R.; Botta, M.; Artico, M.; Corelli, F.; Forte, M.; Caporuscio, F.; Angiolella, L.; Palamara, A. T. *J. Med. Chem.* **2005**, *48*, 5140.

(5) (a) Rani, N.; Sharma, A.; Singh, R. *Mini Rev. Med. Chem.* **2013**, *12*, 1812. (b) Saravanana, S.; Selvana, P. S.; Gopala, N.; Guptab, J. K.; Dec, B. *Arch. Pharm. Chem. Life Sci.* **2005**, *338*, 488. (c) Khabnadideh, S.; Rezaei, Z.; Khalafi-Nezhad, A.; Bahrinajafi, R.; Mohamadia, R.; Farrokhroza, A. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2863.

(6) (a) Abhishek, P.; Kulkarni, C. J.; Tonzola, A. B.; Samson, A. J. *Chem. Mater.* **2004**, *16*, 4556. (b) Wang, Z.; Lu, P.; Chen, S.; Gao, Z.; Shen, F.; Zhang, W.; Xu, Y.; Kwok, H. S.; Ma, Y. *J. Mater. Chem.* **2011**, *21*, 5451.

(7) (a) Bhalla, R.; Helliwell, M.; Garner, C. D. *Inorg. Chem.* **1997**, *36*, 2944. (b) Zhou, L.; Nicholas, K. M. *Inorg. Chem.* **2008**, *47*, 4356. (c) Konishi, H.; Ueda, T.; Muto, T.; Manabe, K. *Org. Lett.* **2012**, *14*, 4722.

(8) Lin, W.; Long, L.; Yuan, L.; Cao, Z.; Chen, B.; Tan, W. *Org. Lett.* **2008**, *10*, 5577.

(9) (a) Takle, A. K.; Brown, M. J. B.; Davies, S.; Dean, D. K.; Francis, G.; Gaiba, A.; Hird, A. W.; King, F. D.; Lovell, P. J.; Naylor, A.; Reith, A. D.; Steadman, J. G.; Wilson, D. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 378. (b) Wang, J.; Mason, R.; Derveer, D. V.; Feng, K.; Bu, X. R. *J. Org. Chem.* **2003**, *68*, 5415. (c) Sarshar, S.; Siev, D.; Mjalli, M. M. *Tetrahedron Lett.* **1996**, *37*, 835. (d) Paul, R.; Brockman, J. A.; Hallett, W. A.; Hanifin, J. W.; Tarrant, M. E.; Torley, L. W.; Callahan, F. M.; Fabio, P. F.; Johnson, B. D.; Lenhard, R. H. *J. Med. Chem.* **1985**, *28*, 1704. (e) Suzuki, H.; Nakaya, C.; Matano, Y. *Tetrahedron Lett.* **1993**, *34*, 1055. (f) Gising, J.; Nilsson, M. T.; Odell, L. R.; Yahiaoui, S.; Lindh, M.; Iyer, H.; Sinha, A. M.; Srinivasa, B. R.; Larhed, M.; Mowbray, S. L.; Karlén, A. *J. Med. Chem.* **2012**, *55*, 2894. (g) Griebenow, N. *Synlett* **2010**, *17*, 2639. (h) Mousset, C.; Olivier, P.; Abdallah, H.; Bignon, J.; Brion, J. D.; Alami, M. *Tetrahedron* **2008**, *64*, 4287. (i) Kim, H. G.; Lee, J. K.; Lee, J. T.; Lee, C. S. *Bull. Korean Chem. Soc.* **2000**, *21*, 345. (j) Mutoh, K.; Shima, K.; Yamaguchi, T.; Kobayashi, M.; Abe, J. *Org. Lett.* **2013**, *15*, 2938. (k) Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 269.

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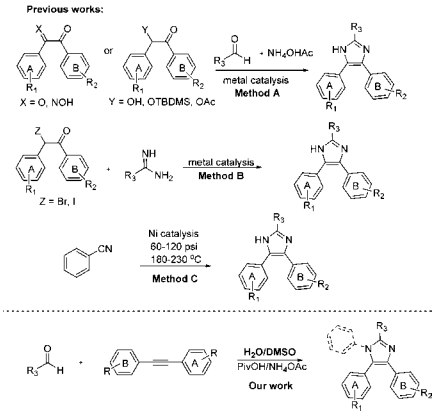
Scheme 1. Synthesis of Imidazole Derivatives with Various Methodologies

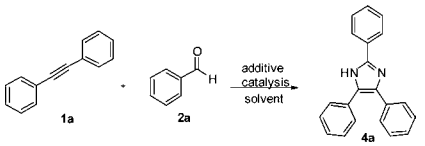


α-hydroxy/acetoxy/silyloxy-ketone as shown in Scheme 1. Moreover, some other reactions were performed with or without using the catalysts under pressure with superheating conditions (Method A, Scheme 1).[10] Apart from these synthetic methods, Lewis acid catalyzed addition reactions with amidines (Method B)[11] and Ni-catalyzed cyclotrimerization (with expulsion of NH_3) of aromatic nitriles under drastic reaction conditions for a prolonged period were also reported in the literature (Method C) .[12]

However, most of these methods suffer from one or more limitations such as harsh reaction conditions, unsatisfactory product yields, tedious isolation procedures, and expensive and detrimental metal precursors, which limit their use under the aspect of environmentally benign processes. Therefore, development of mild, economical, and complementary approaches for 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives is still highly desired due to their extreme significance.

Herein, we report our studies to develop a new approach toward the synthesis of substituted imidazole derivatives using an internal alkyne, aldehyde, and aniline in one pot *via* pivalic acid promoted benzil formation followed by cyclocondensation of amidines through a multicomponent strategy. The synthetic method has an advantage of affording an imidazole core with high structural diversity and excellent reaction yields.

Table 1. Optimization of Reaction Conditions to Synthesize Compound **4a**[a,b]



entry	[O]	solvent	additive	t/°C	yield
1	$KMnO_4$	DMSO	NH_4OAc/ZnO/PivOH	140	–
2	CAN	DMSO	NH_4OAc/ZnO/PivOH	140	trace
3	DMP	DMSO	NH_4OAc/ZnO/PivOH	140	88%
4	PIFA	DMSO	NH_4OAc/ZnO/PivOH	140	76%
5	PIDA	DMSO	NH_4OAc/ZnO/PivOH	140	67%
6	none	DMSO	NH_4OAc/ZnO/PivOH	140	71%
7[c]	none	DMSO	NH_4OAc/ZnO/PivOH	140	84%
8[c]	none	DMSO	NH_4OAc/ZnI_2/PivOH	140	43%
9[c]	none	DMSO	NH_4OAc/$ZnBr_2$/PivOH	140	27%
10[c]	none	DMSO	NH_4OAc/$ZnCl_2$/PivOH	140	31%
11[c]	**none**	**DMSO**	**NH_4OAc/PivOH**	**140**	**83%**
12[c]	none	DMSO	NH_4OH/PivOH	140	65%
13[c]	none	DMSO	NH_4OAc/AcOH	140	32%
14[c]	none	DMSO	NH_4OAc/TFA	140	73%
15[c]	none	DMSO	NH_4OAc/TsOH	140	49%
16[c]	none	DMSO	NH_4OAc/none	140	–
17[c]	none	DMF	NH_4OAc/PivOH	140	33%
18[c]	none	MeCN	NH_4OAc/PivOH	140	–
19[c]	none	PhCl	NH_4OAc/PivOH	140	–
20[c]	none	$CHCl_3$	NH_4OAc/PivOH	140	–
21[c]	none	DMSO	NH_4OAc/PivOH	100	61%
22[c,d]	none	DMSO	NH_4OAc/PivOH	140	65%
23[c,e]	none	H_2O	NH_4OAc/PivOH	140	25%

[a] Reactions were performed with **1a** (1.0 mmol), oxidant (1.0 mmol), additive NH_4OAc (4.0 mmol), ZnO (1.0 mmol), PivOH (1.0 mmol), solvent (DMSO/H_2O = 1:1) at 140 °C for 12 h. [b] Isolated yield. [c] Prolonged reaction time 24 h. [d] Without H_2O. [e] Without DMSO.

In the search for effective conditions, the reaction was carried out with diphenylacetylene (**1a**), benzaldehyde (**2a**) with various oxidants, additives, solvents, and temperatures to form 2,4,5-triphenylimidazole **4a** as summarized in Table 1. The reaction of **1a** with a stoichiometric amount of DMP (Dess-Martin periodinane), $KMnO_4$, and CAN in the presence of NH_4OAc/ZnO/PivOH as an additive in DMSO solvent was carried out at 140 °C, following our previous reported conditions[13] (Table1, entries 1−3). The use of DMP afforded the required product **4a** in 88% yield (entry 3), whereas $KMnO_4$ and ceric (IV) ammonium nitrate (CAN) did not produce the desired product (entries 1−2). Subsequently, by changing the oxidant to PIFA and PIDA, the required product was produced albeit in low yields (entries 4−5). Surprisingly, the desired product **4a** was obtained in the absence of oxidant (entry 6). From the optimistic result of entry 6, we further prolonged the reaction time to 24 h, which then produced

(10) (a) Lantos, I.; Zhang, W.-Y.; Shui, X.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 7092. (b) Teimouri, A.; Chermahini, A. N. *J. Mol. Catal. A: Chem.* **2011**, *346*, 39. (c) Kumar, D.; Kommi, D. N.; Bollineni, N. A.; Patel, R.; Chakraborti, A. K. *Green Chem.* **2012**, *14*, 2038. (d) Sivakumar, K.; Kathirvel, A.; Lalitha, A. *Tetrahedron Lett.* **2010**, *51*, 3018. (e) Wang, L.; Zhong, X.; Zhou, M.; Zhou, W.-Y.; Chen, Q.; He, M.-Y. *J. Chem. Res.* **2013**, *37*, 236. (f) Magee, D. I.; Bahramnejad, M.; Dabiri, M. *Tetrahedron Lett.* **2013**, *54*, 2591. (g) Xu, F.; Wang, N.; Tian, Y.; Li, G. *J. Heterocycl. Chem.* **2013**, *50*, 668. (h) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453. (i) Sparks, R. B.; Combs, A. P. *Org. Lett.* **2004**, *6*, 2473. (j) Chauveau, E.; Marestin, C.; Schiets, F.; Mercier, R. *Green Chem.* **2010**, *12*, 1018. (k) Shelke, K. F.; Sapkal, S. B.; Kakade, G. K.; Shingate, B. B.; Shingare, M. S. *Green Chem. Lett. Rev.* **2010**, *3*, 27.

(11) (a) Wang, L.-M.; Wang, Y.-H.; Tian, H.; Yao, Y.-f.; Shao, J. H.; Liu, B. *J. Fluorine Chem.* **2006**, *127*, 1570. (b) Heravi, M. M.; Bakhtiari, K.; Oskooie, H. A.; Taheri, S. *J. Mol. Catal. A: Chem.* **2007**, *263*, 279.

(12) García, J. J.; Silva, P. Z.; Rios, G. R.; Cresanti, M. G.; Arévalo, A.; Francisco, R. B. *Chem. Commun.* **2011**, *47*, 10121.

(13) Chen, C.-Y.; Hu, W.-P.; Liu, M.-C.; Yan, P.-C.; Wang, J.-J.; Chung, M.-I. *Tetrahedron* **2013**, *69*, 9735.

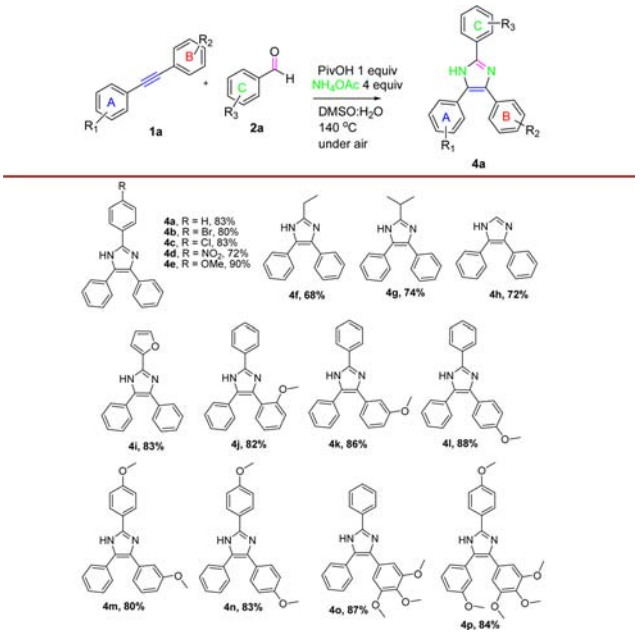


Figure 1. The three components were the series of imidazole derivatives. Reactions were performed with **1** (1.0 mmol), **2** (1.0 mmol), NH_4OAc (4.0 mmol), and PivOH (1.0 mmol) in the presence of a solvent mixture ($DMSO/H_2O$ = 1:1) at 140 °C for 24−40 h. Isolated yields provided.

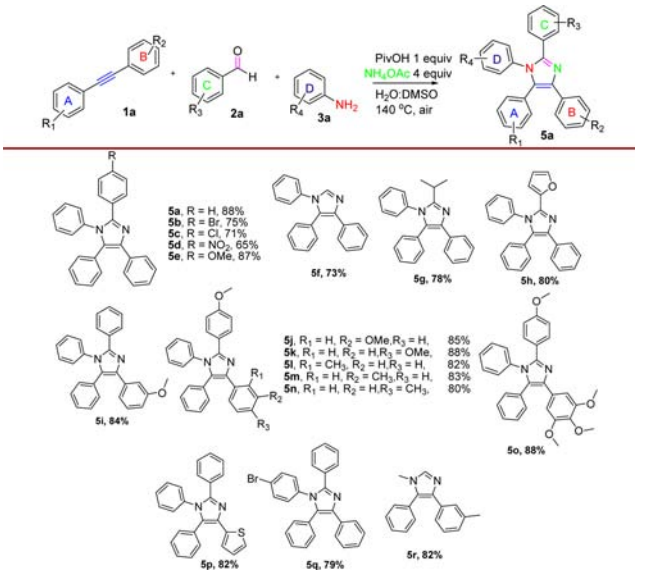


Figure 2. The four components were the series of imidazole derivatives. Reactions were performed with **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), PivOH (1.0 mmol), and NH_4OAc (4.0 mmol) in the presence of a solvent mixture ($DMSO/H_2O$ = 1:1) at 140 °C for 24−48 h. Isolated yields provided.

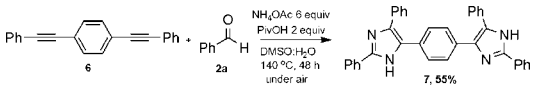
2,4,5-triphenylimidazole **4a** in 84% yield (entry 7). We assumed that the additive ZnO played a crucial role in the reaction. Based on the above reason, we have performed the reaction with various zinc salts, and results show no product formation (entries 8−10). To our delight, the best result was obtained in the absence of ZnO to afford the compound **4a** in 83% yield (entry 11). Furthermore, the ammonia source was investigated by replacing NH_4OAc with NH_4OH, but the yield of product **4a** is not satisfactory (65%, entry 12). With a different acid such as AcOH, TFA (trifluoroacetic acid), TsOH (*p*-toluenesulfonic acid), or without an acid as an additive, the yields were unsatisfactory compared with PivOH (entries 11, 13−16). The feasibility of the reaction was investigated with various solvents (entries 17−20), and it was found that reaction in a dual solvent system ($DMSO/H_2O$ = 1:1) produced the desired target in excellent yield (entry 11). Finally, the reaction was performed without H_2O or DMSO, but there was a decrease in yield of **4a** (entries 22−23). Therefore, the conditions described in entry 11 (4 equiv of NH_4OAc in DMSO and H_2O with PivOH) were found to be optimal.

With the optimized conditions in hand, we have studied the scope and limitations with various alkyl and aryl aldehydes and internal alkynes. In Figure 1, the one-pot approach to synthesize a wide range of imidazole derivatives with various substituents was performed, including electron-withdrawing and -donating functional groups on the aromatic moieties **4a**−**4p**. It is remarkable that the aryl chloride and bromide were compatible substrates **4b**−**4c** with the yield of 80% and 83% respectively, and these molecules will provide a convenient access for metal-catalyzed cross-coupling reactions. Heterocyclic aldehyde (furan-2-carbaldehyde) was well tolerated under similar reaction conditions to obtain the compound **4i** in 83% yield. An electron-donating group at the *ortho*-, *meta*-, and *para*-position of aromatic ring B was also tolerated with an 82−88% yield (**4j**−**4l**). Aliphatic aldehydes were also found to be the best reaction components to be used for the synthesis of compounds **4f**−**4h** in 68−74% yields. In particular, the ring B bearing the 3,4,5-trimethoxy group also proceeded smoothly to afford the desired products **4o**−**4p** in good yields. These products were made with this strategy, because the structure−activity relationship of Combretastatin A4 indicates that the presence of the 3,4,5-trimethoxy group on ring B is fundamental for antitubulin and anticancer activity.[14]

With the success of a three component reaction in hand, we further extended our methodology for the construction of various substituted imidazole scaffolds by utilizing four component reactions. We initiated the feasibility of four component reaction to construct imidazole derivatives; under identical reaction conditions (Table 1, entry 11) with a stoichiometric ratio of aniline derivatives as the fourth component, to our delight, the reaction underwent smooth conversion to obtain the desired compounds in good to excellent yields (Figure 2, **5a**−**r**). Regardless of the electronic

(14) (a) Gaukroger, K.; Hadfield, J. A.; Lawrence, N. J.; Nlan, S.; McGown, A. T. *Org. Biomol. Chem.* **2003**, *1*, 3033. (b) Beale, T. M.; Myers, R. M.; Shearman, J. W.; Charnock-Jones, D. S.; Brenton, J. D.; Gergely, F. V.; Ley, S. V. *Med. Chem. Commun.* **2010**, *1*, 202.

Scheme 2. Synthesis of Dimer Derivative of Imidazole[a,b]



[a] Reaction was performed with **6** (1.0 mmol), **2a** (2.0 mmol), and NH_4OAc (6.0 mmol) in the presence of PivOH (2.0 mmol), in a solvent mixture ($DMSO/H_2O$ = 1:1) at 140 °C for 48 h. [b] Isolated yield.

effect of the substituents on the aromatic rings and nature of aldehydes (**2**), the construction of the scaffold progressed well to obtain the desired molecules **5a**−**5r** in 65−88% yield.

In particular, the D ring bearing an aliphatic group also proceeded smoothly to obtain the corresponding imidazole product (**5r**). The MCR reaction was quite general, as an electron-donating or -withdrawing group or aliphatic substitutent on R_1, R_2, and R_3 was tolerated. Moreover, the structures of **4h**, **5c**, and **5q** were confirmed unambiguously with the help of ORTEP diagram (Supporting Information (SI), Figure S2).

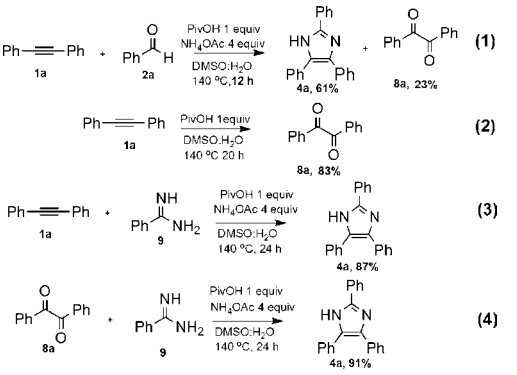
Next, we were curious to know whether diynes undergo this type of reaction because the resulting product would generate imidazole moieties which may find application in medicinal chemistry and OLED devices[15] (Scheme 2). Accordingly, 1,4-bis(phenylethynyl)benzene **6** was carried out with 2 equiv of benzaldehyde under an established procedure. Interestingly, 1-(2,5-diphenyl-1*H*-imidazol-4-yl)-4-(2,4-diphenyl-1*H*-imidazol-5-yl) benzene (**7**) was obtained in 55% yield.

To gain insight into the reaction mechanism, we carried out a few control experiments as shown in Scheme 3. For detailed explanation (Supporting Information (SI), Scheme S1, page S19).

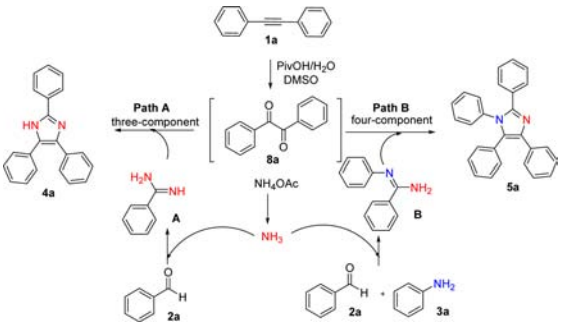
Based on our observations and previous literature,[13,16] a plausible mechanism is outlined in Scheme 4. In the presence of pivalic acid and DMSO the alkynes will be oxidized to generate the intermediate **8a**. Meanwhile, the aldehyde **2a** will react with two molecules of ammonium acetate to give the intermediate **A** (Path A, Scheme 4).[17] Yet, **2a** reacts with one molecule of ammonium acetate and aniline to produce the intermediate **B** (Path B). Both intermediates will undergo a cyclocondensation reaction with **8a** to give the desired products **4a** and **5a**, respectively.

In summary, we have described a simple, efficient, and eco-friendly methodology for the synthesis of imidazole analogues from various internal alkynes, aldehydes, and anilines by a pivalic acid mediated multicomponent reaction. The ambient conditions, easy work-up procedure, and excellent product yields make this methodology an alternative approach to replace the conventional transition metal catalyzed processes. Moreover, the synthesized compounds

Scheme 3. Control Experiments



Scheme 4. Plausible Reaction Mechanism for the Acid-Promoted Construction of Imidazole



were screened with fluorescence emission and UV absorption, and compound **5p**[18,20b] showed the best results compared with the other analogues. This promising molecule **5p** could be a potential candidate for photodynamic therapy (PDT) of skin cancer[19] and organic electroluminescent devices.[6,20]

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Islam, A.; Tsou, C. C.; Hsu, H. J.; Shih, W. L.; Liu, C. H.; Cheng, C. H. *Tamkang Journal of Science and Engineering* **2002**, *5*, 69.

(16) Wan, Z.; Jones, C. D.; Mitchell, D.; Pu, J. Y.; Zhang, T. Y. *J. Org. Chem.* **2006**, *71*, 826.

(17) Kiumars, B.; Mohammad, M. K.; Akbar, N. *Monatsh. Chem.* **2011**, *142*, 159.

(18) (a) Park, S.; Kwon, J. E.; Kim, S. H.; Seo, J.; Chung, K.; Park, S.-Y.; Jang, D.-J.; Medina, B. M.; Gierschner, J.; Park, S. Y. *J. Am. Chem. Soc.* **2009**, *131*, 14043. (b) Baroniya, S.; Anwer, Z.; Sharma, P. K.; Dudhe, R.; Kumar, N. *Der Pharmacia Sinica* **2010**, *1*, 172.

(19) (a) Hu, W.-P.; Chen, Y.-K.; Liao, C.-C.; Yu, H.-S.; Tsai, Y.-M.; Huang, S.-M.; Tsai, F.-Y.; Shen, H.-C.; Chang, L.-S.; Wang, J.-J. *Bioorg. Med. Chem.* **2010**, *18*, 6197. (b) Senadi, G. C.; Hu, W.-P.; Hsiao, J.-S.; Vandavasi, J. K.; Chen, C.-Y.; Wang, J.-J. *Org. Lett.* **2012**, *14*, 4478.

(20) (a) Sarshar, S.; Siev, D.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 835. (b) Satapathy, R.; Wu, Y.-H.; Lin, H.-C. *Org. Lett.* **2012**, *14*, 2564. (c) Li, W.; Lin, W.; Wang, J.; Guan, X. *Org. Lett.* **2013**, *15*, 1768.

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