Base-catalyzed stereoselective intermolecular addition of imidazoles onto alkynes: An easy access to imidazolyl enamines

Monika Patel, Rakesh K. Saunthawal, Akhilesh K. Verma

PII: S0040-4039(13)02198-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.12.100
Reference: TETL 44014

To appear in: *Tetrahedron Letters*

Received Date: 16 October 2013
Revised Date: 25 December 2013
Accepted Date: 26 December 2013

Please cite this article as: Patel, M., Saunthawal, R.K., Verma, A.K., Base-catalyzed stereoselective intermolecular addition of imidazoles onto alkynes: An easy access to imidazolyl enamines, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2013.12.100

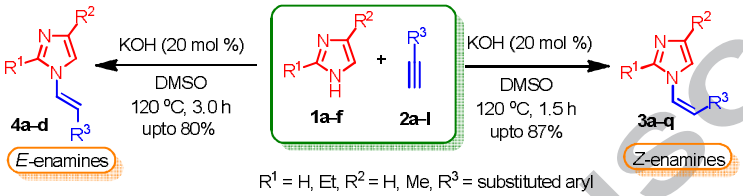
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Base-catalyzed stereoselective intermolecular addition of imidazoles onto alkynes: An easy access to imidazolyl enamines

Leave this area blank for abstract info.

Monika Patel, Rakesh K. Saunthawal and Akhilesh K. Verma*



Tetrahedron Letters
journal homepage: www.elsevier.com

Base-catalyzed stereoselective intermolecular addition of imidazoles onto alkynes: An easy access to imidazolyl enamines

Monika Patel, Rakesh K. Saunthawal and Akhilesh K. Verma*

Synthetic Organic Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110007, India

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Hydroamination, Alkyne
Enamines, Imidazole
Stereoselective, N-Heterocycles, Regioselective

ABSTRACT

An efficient transition metal-free approach for the regio- and stereoselective addition of imidazoles **1a–f** onto alkynes **2a–l** to provide the *Z*- and *E* isomers of imidazolyl enamines **3a–q** and **4a–d** using catalytic amount of KOH is described. Stereoselectivity of the addition products (*Z* and *E* isomer) was found to be dependent upon time. Competitive experiments show that imidazole is less reactive than pyrrole and more reactive than aniline towards hydroamination.

Nitrogen-containing molecules such as imidazoles are an important class of heteroaromatic compounds due to their presence in biologically active,[1] pharmaceuticals and natural products[2]. Imidazole nucleus is commonly found in biomolecules and amino acids such as biotin, purine, histidine, histamine, pilocarpine alkaloids,[3] and other alkaloids, which have shown to display remarkable biological activities i.e. anticryptococcal, antimicrobial and various other cytotoxic activities.[4] The medicinal properties of imidazole which possess broad spectrum of physiological and biological activities mainly includes antibacterial,[5] antifungal,[6] and antimalarial activity.[7] Imidazole derivatives, for instant nitro-vinylimidazole (**i**),[8] etomidate (**ii**), and ketoconazole (**iii**) are common structural arrays that are involved in a variety of inflammatory and immunological disorders and also comprise an important application in drug therapy.[9]

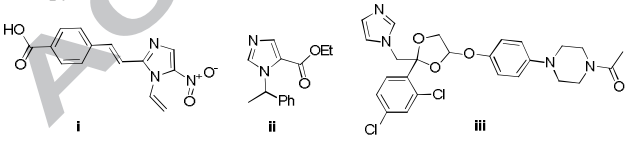


Figure 1. Biologically active imidazole derivatives.

Hydroamination of alkynes represent an attractive approach for the synthesis of nitrogen heterocycles, enamines and imines. Inter- and intramolecular addition of alkynes onto aryl amines using metal complexes has been well studied by Bergman,[10] Doye,[11] Beller,[12] Yamamoto,[13] Knochel,[14] Ackermann,[15] Kondo,[16] Kozmin[17a] (Figure 2, i) and others;[17]

* Corresponding author. Tel.: +91 1127666646 (Ext. 175)
E-mail address: averma@acbr.du.ac.in (Akhilesh K. Verma)

However in contrast, addition of *N*-heterocycles onto alkynes has not been much explored. Knochel in 1999 reported the first example for the addition of *N*-heterocycles onto phenylacetylene using $CsOH.H_2O$ (Figure 2, ii). Recently we[18] and Trofimov[19] reported the base-mediated addition of electron-rich *N*-heterocycles (indoles and pyrroles) onto alkynes.

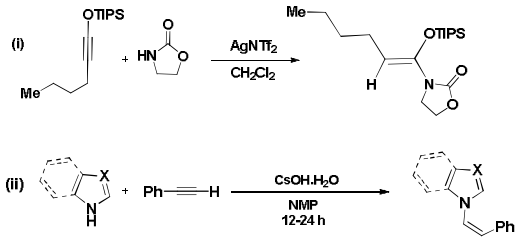
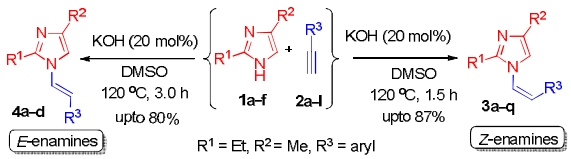


Figure 2. (i) Hydroamination of alkynes using metal catalyst. (ii) First hydroamination reported by Knochel.

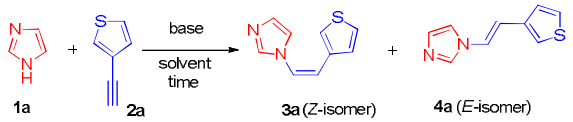
With this limited work on hydroamination of *N*-heterocycles on alkynes and as a part of our ongoing research on alkyne chemistry,[20] herein, we wish to report transition metal-free hydroamination of electron-deficient imidazoles onto alkynes. (Scheme 1).



Scheme 1. Synthesis of *Z*-styryl enamines and *E*-styryl enamines.

In order to optimize the reaction condition for the reaction, previously reported catalyst and reaction conditions for the hydroamination[18] of electron-rich heterocycles on alkynes, was examined in the reaction of imidazole **1a** with 3-ethynylthiophene **2a** (Table 1). When 20 mol % of KOH was used as a catalyst in DMSO at 120°C for 0.5 h, (*Z*)-1-(2-(thiophen-3-yl)vinyl)-1*H*-imidazole **3a** was obtained in only 35% yield (Table 1, entry 1). Increase in the reaction time from 0.5 h to 1 h and then to 1.5 h, afforded the *Z*-addition product **3a** in 62% and 84% yields respectively (entries 2–3). When reaction was allowed to stir for 2 h, it led to the conversion of kinetically stable Z-isomer into thermodynamically stable *E*-isomer (entries 4–5). We observed that after running the reaction for 3 h, products **3a** (*Z*-isomer) and **4a** (*E*-isomer) were obtained in 10:90 stereoselectivity (entry 6). The similar result was obtained when the reaction was run for 5 h (entry 7). Lowering the catalyst loading from 20 mol % to 10 mol % provided the addition product **3a** in 59% yield (entry 8). Decrease in the reaction temperature adversely affected the yield of the addition product (entries 9–12). Using DMF and NMP as a solvent, the product **3a** was obtained in 30% and 45% yields respectively (entries 13–14). No addition product was obtained when toluene and DMA were used (entries 15–16). Use of CsOH provided the desired product **3a** in 60% yield (entry 17).

Table 1. Optimization of reaction conditions[a]



Entry[a]	Base (equiv)	Solvent	Time (h)/ T °C	Yield (%)[b] 3a(*Z*):4a(*E*)	
1	KOH/0.2	DMSO	0.5/120	35	100:00
2	KOH/0.2	DMSO	1.0/120	62	100:00
3	**KOH/0.2**	**DMSO**	**1.5/120**	**84**	**100:00**
4	KOH/0.2	DMSO	2.0/120	78	74:26
5	KOH/0.2	DMSO	2.5/120	76	35:65
6	**KOH/0.2**	**DMSO**	**3.0/120**	**80**	**10:90**
7	KOH/0.2	DMSO	5.0/120	77	10:90
8	KOH/0.1	DMSO	1.5/120	59	100:00
9	KOH/0.2	DMSO	1.5/60	10	100:00
10	KOH/0.2	DMSO	1.5/80	30	100:00
11	KOH/0.2	DMSO	3.0/80	42	95:05
12	KOH/0.2	DMSO	3.0/100	60	90:10
13	KOH/0.2	DMF	1.5./120	30	100:00
14	KOH/0.2	NMP	1.5/120	45	100:00
15	KOH/0.2	Toluene	1.5/110	-	-
16	KOH/0.2	DMA	1.5/120	-	-
17	CsOH/0.2	DMSO	1.5/120	60	100:00

[a] Reactions were performed using 2.0 equiv of imidazoles **1a**, 1.0 mmol of the alkyne **2a**, and base in 1.5 mL of solvent.
[b] Isolated yield.

The scope and limitations of the optimized reaction conditions were next examined by using various substituted terminal alkynes **2a–i** and imidazoles **1a–c** (Table 2). The presence of electron-releasing thiophene, methyl and methoxy groups on alkyne substrates afforded the addition products **3a–f** in 79–87% yields (entries 1–6). However, alkynes having *n*-butyl substitution and electron-withdrawing group provided the desired corresponding addition products **3g–h** in moderate yields (entries 7–8). Reaction of imidazole with phenylacetylene **2i** provided the Z-styryl product **3i** in 80% yield (entry 9). Unsymmetrically substituted imidazoles are well known for the rapid tautomerization (Figure 3).[7d] When 4-methyl-imidazole **1b** was used, mixtures of tautomeric addition products were obtained (entries 10–11) (Figure 3). Interestingly, when 2-ethyl-4- methyl-1*H*-imidazole **1c** was reacted with alkyne **2j**, only (*Z*)- styryl-

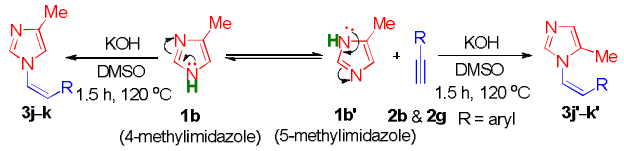
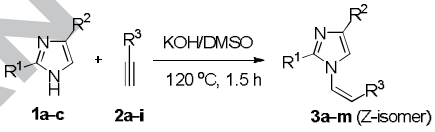


Figure 3. Tautomerization in 4-methylimidazole.

imidazole **3l** was obtained in 70% yield (entry 12). However the reaction of **1c** with phenylacetylene **2i** provided the mixture of *E* and *Z*-styryl product **3m** in 82% yield (entry 13). No tautomeric alkenylation was observed with imidazole **1c**, the probable reason for the above fact might be due to the steric hindrance of the methyl and ethyl groups present adjacent to the rear nitrogen.
Reaction of benzimidazole **1d** with electron-rich alkynes **2b–c** provided the addition products **3n–o** in 81% and 79% yields respectively (entries 14-15). When of 2-methylimidazole **1e** (a regioisomer of **1b**) was reacted with alkyne **2i** and **2e**, products **3p–q** were obtained in 75% and 70% yield respectively (entries 16–17). However no desired addition product was obtained when electron-withdrawing 4-nitroimidazole **1f** was used as the reactant (entry 18). The reactant **1f** remained unchanged even with longer reaction time.

Table 2. Synthesis of *Z*- styrylimidazoles.



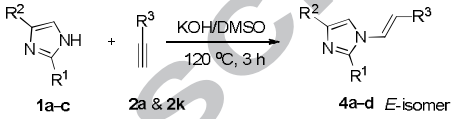
Entry[a]	Imidazole	Alkyne	Product	Yield (%)[b]
1	**1a**	**2a**	**3a**	84
2	**1a**	**2b**	**3b**	82
3	**1a**	**2c**	**3c**	87
4	**1a**	**2d**	**3d**	80
5	**1a**	**2e**	**3e**	85
6	**1a**	**2f**	**3f**	79
7	**1a**	**2g**	**3g**	76

8	**1a**	**2h**	**3h**	70
9	**1a**	**2i**	**3i**	80
10	**1b**	**2b**	**3j** + **3j'**	80 (50:50)
11	**1b**	**2g**	**3k** + **3k'**	71 (50:50)
12	**1c**	**2j**	**3l**	70
13	**1c**	**2i**	**3m**	82 (50:50)
14	**1d**	**2b**	**3n**	81[c]
15	**1d**	**2c**	**3o**	79[c]
16	**1e**	**2i**	**3p**	75[c]
17	**1e**	**2e**	**3q**	70[c]
18	**1f**	**2i**	**NR**	**NR**[c]

[a] Unless otherwise noted, reactions were performed using 2.0 equiv of imidazoles **1**, 1.0 mmol of the alkyne **2**, and KOH (20 mol %) in 1.5 mL of DMSO at 120°C for 1.5 h.
[b]Isolated yield.
[c] Reaction was run for 3.0 h.
[d] Reaction was run for 8.0 h.

During the optimization studies we observed that formation of *E* and *Z* isomer depended upon reaction time. In Table 2, we have reported the synthesis of *Z*-addition products. To further extend the scope of the developed chemistry *E*-styrylimidazoles **4a–d** were synthesized by tuning the reaction time by reacting alkyne **2a** and **2k** with imidazoles **1a–c** using KOH in DMSO at 120 °C for 3 h (Table 3). Alkyne **2a** bearing electron-rich thiophene ring afforded the *Z*-addition product **3a** in 84% yield in 1.5 h; however after running the reaction for 3 h afforded the *E*-addition product **4a** in 80% yield. Alkyne **2k** with an electron-withdrawing CF_3 group on aryl ring provided the *E* addition products **4b–d** comparatively in lower yields (entries 2–4). Unfortunately when the reaction of **1e** was performed using open chain aliphatic alkyne **2l**, no addition product was obtained (entry 5).

Table 3. Synthesis of *E*-styrylimidazoles



1a–c **2a & 2k** **4a–d** *E*-isomer

Entry[a]	Imidazoles	Alkynes	Product	Yield(%)[b]
1	**1a**	**2a**	**4a**	80[c]
2	**1a**	**2k**	**4b**	72
3	**1b**	**2k**	**4c**	73
4	**1c**	**2k**	**4d**	71
5	**1e**	**2l**	**NR**	**NR**

[a] Reactions were performed using 2.0 equiv of Imidazoles **1**, 1.0 mmol of the alkyne **2**, and KOH (20 mol %) in 1.5 mL DMSO at 120 °C for 3 h.
[b]Isolated yield.
[c] Along with 10% of *Z*- isomer.

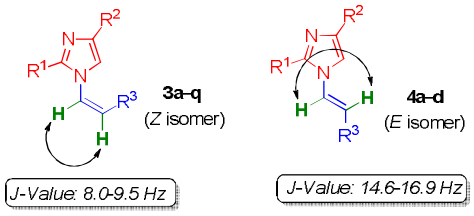
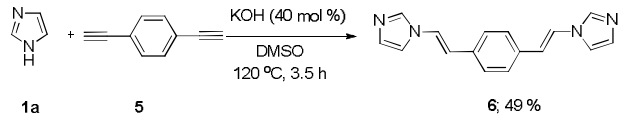


Figure 4. *Z* and *E* Stereoselectivity.

The *Z* and *E* stereoselectivity in the product was characterized by the coupling constant of the styryl protons in ^{1}H NMR

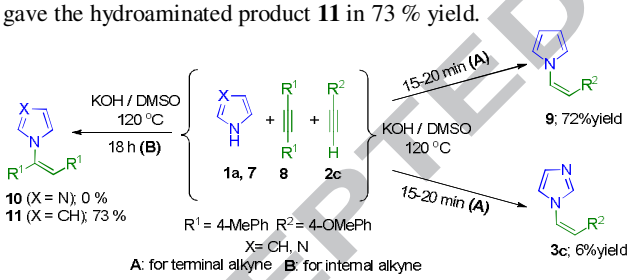
spectroscopy. The *J*-value of the two styryl protons in products **3a–q** lies between 8.0–9.5 Hz which supports the *Z*-stereoselectivity in the products; however products **4a–d** with coupling constant between 14.6–16.7 Hz conforms the *E*-stereoselectivity in the addition products (Figure 4).



Scheme 2. Hydroamination with dialkyne.

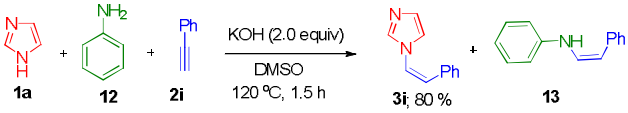
We further explore the possibility of the reaction with a dialkyne. More fascinatingly, when 1,4-diethynylbenzene **5** was reacted with 4.0 equiv of **1a** using KOH (40 mol %) at 120 °C, for 3.5 h, the thermodynamically stable 1,4-bis((*E*)-2-(1*H*-imidazol-1-yl)vinyl)benzene **6** was obtained in 49% yield (Scheme 2). Reaction monitoring at incessant interval of time showed that the addition of the imidazole onto alkyne takes place very rapidly, leading to the transformation of kinetically stable *Z*-isomer to thermodynamically stable *E*-isomer followed by the attack on another alkyne group present in the substrate **5**.

In order to validate the reactivity behavior of the imidazole **1a** and pyrrole **7** on alkyne, we performed a control experiment. We carried out the reaction of **1a** (2.0 equiv), pyrrole (2.0 equiv), with alkyne **2c** (1 mmol) using 20 mol % of KOH in 2 mL of DMSO at 120 °C for 15 min (Scheme 3). The results demonstrate that the product **9** (addition of pyrrole on alkyne) was obtained in 72% yield, whereas product **3c** (addition of imidazole on alkyne) was formed only in 6% yield. This clearly reveals that imidazole **1a** is less reactive than pyrrole and afforded the products in lower yields along with unreacted alkyne. When the hydroamination was performed using internal alkyne **8**, imidazole fails to afford the desired addition product **10**; however highly reactive pyrrole gave the hydroaminated product **11** in 73 % yield.



Scheme 3. Competitive study between pyrrole and imidazole.

To further confirm the reactivity behavior between imidazole **1a** and arylamine **12** we performed another control experiment. We carried out the reaction of **1a** (1 mmol), aniline **12** (1 mmol), with alkyne **2i** (1 mmol) using 20 mol % of KOH in 2 mL of DMSO at 120 °C for 1.5 h (Scheme 4). The results demonstrate that the product **3i** (addition of imidazole on alkyne) was obtained in 80% yield, whereas product **13** (addition of aniline on alkyne) was not formed. This clearly reveals that hydroamination of imidazole is preferred over arylamine.



Scheme 4. Competitive study between imidazole and aniline.

In conclusion, we have described an efficient approach for the regio-and stereoselective addition of imidazoles (electron-deficient heterocycle) onto alkynes to provide a broad range of synthetically and biologically important (*Z*)- and (*E*)-imidazolyl enamines selectively in good yields. This transition-metal and ligand-free methodology utilizes a basic system of KOH/DMSO for the addition of imidazoles onto alkynes. The competitive experiments clearly demonstrates that imidazole is less reactive than pyrrole and more reactive than aniline. From a synthetic point of view, the developed approach is general, cost effective and could be used for the synthesis of vide range of imidazolyl enamines of biological importance.

Acknowledgments

We thank CSIR and DU-DST-PURSE grant for the financial support and USIC, University of Delhi for the use of Instrumentation facility. MP and RKS are thankful to DST and UGC for Fellowship.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.125.

References and notes

(1) (a) Chen, P.; Barrish, J. C.; Iwanowicz, E.; Lin, J.; Bednarz, M.S.; Chen, B. *Tetrahedron Lett.* **2001**, *42*, 4293; (b) Greenhill, J. V.; Lue, P. *Prog. Med. Chem.* **1993**, *30*, 203; (c) Sullivan, J. D.; Giles, R. L.; Looper, R. E. *Curr. Bioact. Compd.* **2009**, *5*, 39; (d) Iradyan, M. A.; Iradyan, N. S.; Arsenyan, F. G.; Stepanyan, G. M. *Pharm. Chem. J.* **2009**, *43*, 439; (d) Jin, Z. *Nat. Prod. Rep*. **2009**, *26*, 382; (e) Ebada, S. S.; Proksch, P. *Mini Rev. Med. Chem.* **2011**, *11*, 225.

(2) (a) Kobayashi, J.; Ishibashi, M. *Alkaloids* **1992**, *41*, 41; (b) Kobayashi, J. Ishibashi, M. *Compr. Nat. Prod Chem.* **1999**, *8*, 415; (c) Blunt, J. W.; Copp B. R.; Keyzers, R. A. *Nat. Prod. Rep.* **2013**, *30*, 237; (d) Berlinck, R. G. S.; Burtoloso, A. C. B.; Silva, A. E.; Romminger, S.; Morais, R. P.; Bandeira, K.; Mizuno, C. M. *Nat. Prod. Rep.* **2012**, *29*, 1382.

(3) Grimmett, M. R. *Comprehensive Heterocyclic Chemistry II*; Katritsky, A. R.; Scriven, E. F. V., Eds.; Pergamon: Oxford. **1996**, *3*, 77.

(4) Luca, L. D. *Curr. Med. Chem.* **2006**, *13*, 1.

(5) Bhandari, K.; Srinivas, N.; Keshava, G.B.S.; Shukla, P. K. *Eur. J. Med. Chem.* **2009**, *44*, 437.

(6) (a) Niwano, Y.; Seo, A.; Kanai, K.; Hamaguchi, H.; Uchida, K.; Yamaguchi, H. *Antimicrob. Agents Chemother.* **1994**, *38*, 2204. (b) Di Santo, R.; 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; (c) Botta, M.; Corelli, F.; Gasparrini, F.; Messina, F.; Mugnaini, C. *J. Org. Chem.* **2000**, *65*, 4736. (d) Saha, A. K.; Liu, L.; Simoneaux, R. L.; Kukla, M. J.; Marichal, P.; Odds, F. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2175.

(7) (a) Katritzky A. R.; Rees. *Comprehensive Heterocyclic Chemistry,* **1984**, *5*, 469; (b) Grimmett, M. R. Imidazole Benzimidazole Synthesis Academic Press **1997**; (c) Brown, E. G. *Ring Nitrogen and Key Biomolecules. Kluwer Academic Press*, **1998**; (d) Pozharskii, A.F, et al. *Heterocycles in Life and Society. John Wiley & Sons*. **1997**. (e) Congiu, C.; Cocco, M. T.; Onnis, V. *Bioorg. & Med. Chem. Lett.* **2008**, *18*, 989; (f) Venkatesan, A. M.; Agarwal, A.; Abe T.; Ushirogochi, H.O.; Santos, D.; Li, Z.; Francisco, G.; Lin, Y. I.; Peterson, P.J.; Yang, Y.; Weiss, W. J.; Shales, D. M.; Mansour, T.S. *Bioorg. Med. Chem.* **2008**, *16*, 1890; (g) Nakamura, T.; Kakinuma, H.; Umemiya, H.; Amada, H.; Miyata, N.; Taniguchi, K.; Bando, K.; Sato, M. *Bioorg. & Med. Chem. Lett.* **2004,** *14*, 333; (h) Han, M. S.; Kim, D. H. *Bioorg. & Med. Chem. Lett.* **2001**, *11*, 1425; (i) Roman,

G.; Riley, J.G.; Vlahakis, J. Z.; Kinobe, R. T.; Brien, J. F.; Nakatsu, K.; Szarek, W.A. *Bioorg. Med. Chem.* **2007**, *15*, 3225; (j) Bbizhayev, M. A. *Life Sci.* **2006**, *78*, 2343; (k) Nantermet, P.G.; Barrow, J. C.; Lindsley, S. R.; Young, M.; Mao, S.; Carroll, S.; Bailey, C.; Bosserman, M.; Colussi, D.; McMasters, D. R.; Vacca, J. P.; Selnick, H. G.; *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2141; (l) Adams, J. L.; Boehm, J. C.; Gallagher, T. F.; Kassis, S.; Webb, E. F.; Hall, R.; Sorenson, M.; Garigipati, R.; Griswold, D. E.; Lee, J. C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2867.

(8) Ross, W. J.; Jamieson, W. B.; McCowen, M. C. *J. Med. Chem.* **1973**, *16*, 347.

(9) (a) Wilson, Gisvold's Textbook of *Organic Medicinal and Pharmaceutical Chemistry*, 10th ed.; Delgado, J. N., Remers, W. A. Eds.; *Lippincott-Raven: Philadelphia*, PA. **1998**; (b) Coura, J. R.; Castro, S. L. *Mem. Inst. Oswaldo Cruz.* **2002**, *97*, 3.

(10) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923.

(11) (a) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, *2003*, 935; (b) Heutling, A.; Doye, S. *J. Org. Chem.* **2002**, *67*, 1961.

(12) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795.

(13) Lutete, L. M.; Kadota, I; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622.

(14) (a) Rodriguez, A.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488; (b) Koradin, C.; Dohle, W.; Rodriguez, A.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571; (c) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193.

(15) (a) Ackermann, L.; Song, W.; Sandmann, R. *J. Organomet. Chem.* **2011**, *696*, 195; (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 439; (c) Kaspar, L. T.; Ackermann, L. *Tetrahedron* **2005**, *61*, 11311; (d) Ackermann, L.; Sandmann, R.; Kondrashov, M. V. *Synlett* **2009**, *8*, 1219; (e) Ackermann, L.; Barfußer, S.; Potukuchi, H. K. *Adv. Synth. Catal.* **2009**, *346*, 1064.

(16) Imahori, T.; Hori, C.; Kondo, Y. *Adv. Synth. Catal.* **2004**, *346*, 1090.

(17) (a) Sun, J; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4991; (b) Zhang, Y; Donahue, J. P.; Li, C.J. *Org. Lett.* **2007**, *9*, 627.

(18) (a) Verma, A. K.; Joshi, M.; Singh, V. P. *Org. Lett.* **2011**, *13*, 1630; (b) Joshi, M.; Tiwari, R.; Verma, A. K. *Org. Lett.* **2012**, *14*, 1106; (c) Joshi, M.; Patel, M.; Tiwari, R.; Verma, A. K. *J. Org. Chem.* **2012**, *77*, 5633; (d) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 1138.

(19) Dvorkoa, M. Y.; Schmidt, E.Y.; Glotovaa, T. E.; Shabalin, D. A.; Ushakov, I. A.; Kobychev, V. B.; Petrushenkoa, K. B.; Mikhaleva A. I.; Trofimov, B. A. *Tetrahedron* **2012**, *68*, 1963.

(20) (a) Verma, A. K.; Aggarwal, T.; Rustagi, V.; Larock, R. C. *Chem. Commun.* **2010**, *46*, 4064; (b) Verma, A. K.; Shukla, S. P.; Singh, J.; Rustagi, V. *J. Org. Chem.* **2011**, *76*, 5670; (c) Rustagi, V.; Aggarwal, T.; Verma, A. K. *Green Chem.* **2011**, *13*, 1640; (d) Aggarwal, T.; Imam, M.; Kaushik, N. K.; Chauhan, V. S.; Verma., A. K. *ACS Comb. Sci.* **2011**, *13*, 530.

(21) *General procedure for the synthesis of substituted Z-styryl-1H-imidazole* **(3b)**. An oven-dried Schlenk tube with a teflon screw valve was charged with 2.0 equiv of imidazole **1a–c**, 1.0 mmol of the alkyne **2b**, and KOH (20 mol %) in DMSO (2.0 mL). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with nitrogen. The reaction mixture was heated to 120 °C until alkyne **2b** had been completely consumed (as determined by TLC) and was allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (ethylacetate and hexane 4:6). *(Z)-1-(4-Methylstyryl)-1H-imidazole* **(3b)**.The product was obtained as orange semi-solid : ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.99 (s, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.82 (s, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 6.28 (d, *J* = 9.5 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 136.8, 130.5, 129.3, 129.2, 128.3, 123.8, 121.6, 118.4, 21.1. HRMS ESI: [M+] Calcd for $C_{12}H_{12}N_2$: 184.1000; found: 184.1002.