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Complete List of Authors:	LIKHAR, PRAVIN; Indian Institute of Chemical Technology, IandPC Dept Karkhelikar, Manjusha; IICT, Organomet.Gp., I&PC Division Jha, Rajeev; University of Delhi, Chemistry Balasubramanian, Sridhar; Indian Institute of Chemical Technology, Verma, Akhilesh; University of Delhi, Chemistry

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ARTICLE TYPE

An Expedient Approach to Pyrrolo[3,2-*c*]quinolines via Regioselective Formation of Pyrrole Nucleus over Indoles

Manjusha V. Karkhelikar,[a] Rajeev R. Jha,[b] B. Sridhar,[c] Pravin R. Likhar*[a] and Akhilesh K. Verma*[b]

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An efficient approach for the synthesis of pyrrolo[3,2-*c*]quinolines (core nucleus of natural product martinellic acid) from protected 2-alkynylanilines via regioselective formation of pyrroles followed by Heck and intramolecular Michael addition has been described.

The pyrrolo[3,2-*c*]quinolines are chemically interesting molecules because the core structure is frequently found in martinellic acid and biologically active angular tricyclic heterocycles.[1] The applications and synthetic interest of core structures as non-peptide antagonists for bradykinin receptor was recently renewed.[2]

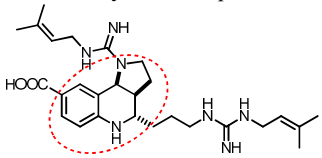
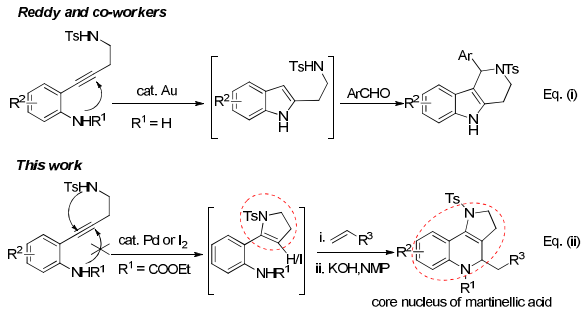


Figure 1. Structure of martinellic acid

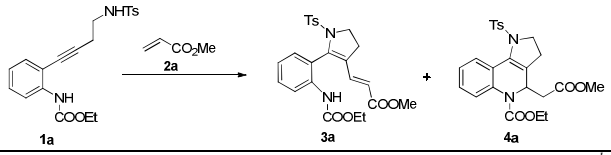
In recent years electrophilic cyclization of alkynes has emerged as an effective protocol in the synthesis of variety of heterocyclic compounds.[3] The protocol exemplifies the synthesis of large number of diverse heterocycles which have found ample applications in biological as well as material chemistry.[4] In general, these cyclization reactions are highly efficient, performed under mild conditions and compatible with variety of functional groups. The success of cyclization in diarylalkynes bearing competitive nucleophiles depends upon the nucleophilicity of functional groups and steric effects.[5] A literature survey revealed that electrophilic cyclization of alkynes has been well explored for the synthesis of wide variety of heterocycles; however, competitive electrophilic cyclization of alkynes bearing two nucleophiles has not been much explored. Reddy and co-workers recently reported tandem synthesis of 2,3,4,5-tetrahydro-1*H*-pyrido [4,3-*b*]indoles from 2-(4-aminobut-1-yn-1-yl)anilines via in situ generation of 2-alkylindoles (eq i). The competitive nature of both the amine groups in the formation of indole derivatives as well as pyrrole derivatives has not been demonstrated in the literature so far.[6]

In continuation of our ongoing work on synthesis of heterocycles by electrophilic cyclization of alkynes,[7] in this study we observed that electronic modification in amine groups (attached to aromatic rings) alters the nucleophilic attack of amino group and favoured selective formation of the pyrrole nucleus over



indoles (eq ii). The present study highlight the synthesis of pyrrolo[3,2-*c*]quinolines (core nucleus of the natural product martinellic acid) via selective formation of a pyrrole intermediate over indoles starting from easily accessible 2-(4-aminobut-1-yn-1-yl)anilines. Recently, Wada and co-workers reported the selective synthesis of pyrrole and dihydropyrrole from α-propargylic glycine.[8]

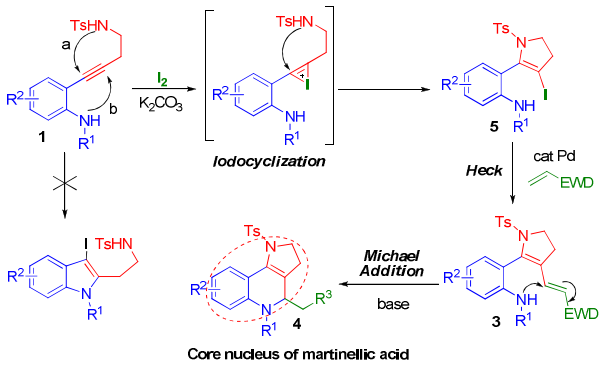
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (mol %)	Oxidant	Solvent	*T* (°C)/ Time (h)	Yield(%)[b] **3a**	**4a**
1	$Pd(OAc)_2$/5	$Cu(OAc)_2$	MeCN	50/4	17	00
2	$Pd(OAc)_2$/10	$Cu(OAc)_2$	MeCN	75/10	23	00
3	$PdCl_2$/ 10	$Cu(OAc)_2$	MeCN	75/18	41	05
4	$Pd(PPh_3)_2Cl_2$/10	$Cu(OAc_2$	MeCN	75/18	30	00
5	$Pd(PPh_3)_4$/10	$Cu(OAc)_2$	MeCN	75/18	30	00
6	$PdCl_2$/ 10	$CuCl_2$	MeCN	75/18	44	07
7	$PdCl_2$/ 10	Ag_2O	MeCN	75/18	26	00
8	$PdCl_2$/ 10	$(C_6H_5CO)_2O_2$	MeCN	75/18	21	00
9	$PdCl_2$/ 10	$CuCl_2$	MeCN	75/18	35	06[c]
10	$PdCl_2$/ 10	$CuCl_2$	MeCN	75/18	33	08[d]
11	**$PdCl_2$/ 10**	**$CuCl_2$**	**DMF**	**120/18**	**58**	**12**
12	$PdCl_2$/ 10	$CuCl_2$	DMF	120/18	11	00[e]

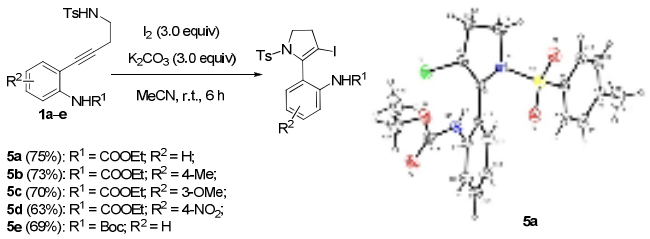
[a] Reaction was performed using 0.5 mmol of **1a**, acrylate **2a** (1.0 mmol), 2.0 equiv of oxidant, 2.0 equiv of NaOAc, 2.0 equiv TBAF in 2.0 mL of solvent. [b] Isolated yields. [c]Using KOH, [d]Using NaOH, [e]Reaction without TBAF.

To identify the most favourable conditions for the designed reaction, variety of catalysts, oxidants and solvents were examined in the reaction of **1a** with methyl acrylate **2a** (Table 1). When 5 mol % of $Pd(OAc)_2$, 2.0 equiv of $Cu(OAc)_2$ and 2.0 equiv of NaOAc was used in 2.0 mL of MeCN at 50 °C for 4 h, only 17% of compound **3a** (pyrrole intermediate) was obtained (Table 1, entry 1). Increase of catalyst loading, temperature and time of the reaction marginally improved the yield of product **3a** (Table 1, entry 2). Use of $PdCl_2$ and increase in reaction time afforded the product **3a** in 41% yield along with the formation of product **4a** (Table 1, entry 3). Screening of other palladium catalysts and oxidants such as $CuCl_2$, Ag_2O and $(C_6H_5CO)_2O_2$ could not improve the yield of **3a** and **4a** (Table 1, entries 4–8). Similarly, by changing the base to NaOH and KOH, the yield of pyrrole could not improve (Table 1, entries 9–10). Among the solvents tested, DMF was found to be effective for the reaction. The best result was obtained using 10 mol % of $PdCl_2$, 2.0 equiv of $CuCl_2$ in DMF at 120 °C (Table 1, entry 11). No reaction was observed in the absence of TBAF (entry 12). (see supporting information for the other screening parameters)



Scheme 1 Alternate route for the synthesis of martinellic acid core.

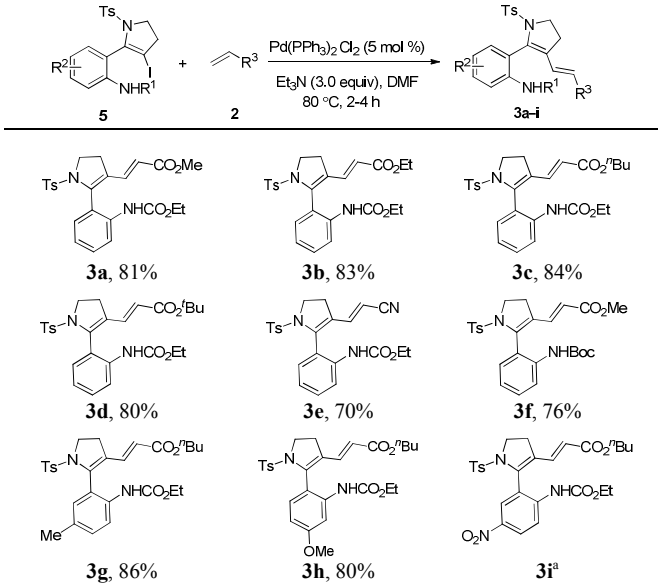
After observing the lower yields of the products, we changed our strategy to improve the yields of the martinellic core nucleus **4a**. Lower yield of the product **4a** possibly could be due to the strength of base employed along with palladium. In our new approach, we first followed the electrophilic iodocyclization[9] to synthesize the iodocyclized compound **5** from **1**. Having iodo substitution at the 3-position of pyrrole, we had an opportunity to prepare compound **4**, using the reported Heck coupling followed by Michael addition (Scheme 1).



Scheme 2. Iodine-mediated selective synthesis of pyrroles.

Iodo-substituted pyrroles **5a–e** were obtained in good yields using 3.0 equiv of iodine and 3.0 equiv of K_2CO_3 in acetonitrile at room temperature (Scheme 2).[10] It is interesting to note that cyclization took place regioselectively and afforded iodo-substituted pyrroles **5** over iodo-substituted indoles by the preferential nucleophilic attack of the amino group of NHTs onto alkynes. All the iodocyclized compounds were fully characterized by ^1H NMR, ^{13}C NMR and HRMS. The structure of compound **5a** was further confirmed by X-ray crystallographic studies.

Heck coupling products **3a–i** were obtained in good to excellent yields by the reaction of iodo-substituted pyrrole **5a–e** with alkenes **2a–d** using 5 mol % $PdCl_2(PPh_3)_2$ and 3.0 equiv of Et_3N in DMF at 80 °C (Scheme 3).



[a] Not isolated.

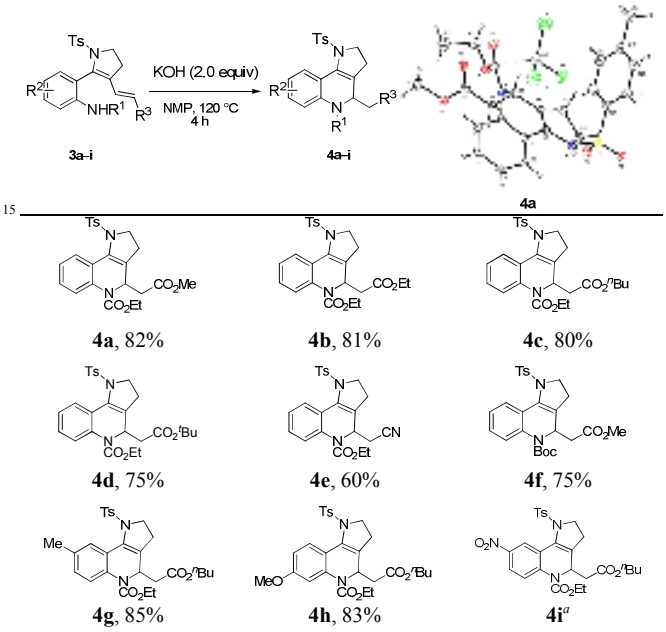
Scheme 3. Palladium-catalyzed Heck coupling reactions

Acrylates **2a–d** provided the coupling products **3a–d** in 80–84% yields; however, acrylonitrile **2e** afforded the product **3e** in 70% yield. In the case of Boc-protected anilines, a 76% yield of the desired product **3f** was obtained. The electron-releasing methyl and methoxy group on the *para* and *meta*-position of the phenyl group afforded the desired product **3g** and **3h** in 86 and 80% yields, respectively. The nitro-substituted substrate also afforded the product **3i;** however we could not isolate the desired product due to decomposition during chromatographic separation. The crude product was used for the next step. The formation of compound **3i** was confirmed by GC and GCMS.

To obtain pyrrolo[3,2-c]quinolines **4a–i**, we optimized[10] the reaction condition for the designed intramolecular aza-Michael reaction. The use of 2.0 equiv of KOH in *N*-methyl pyrrolidine at 120 °C for 4 h (optimized condition) afforded the desired products **4a–i** in good to excellent yields (Scheme 4). The tricyclic fused heterocycle **4a** was characterized by ^1H, ^{13}C NMR, HRMS and finally confirmed by X-ray crystallographic studies.

Variety of pyrrolo[3,2-*c*]quinolines were synthesized by varying the substitution in the starting substrates. No substantial change in the yields of the products was found by changing the

protecting groups of the amines (Scheme 4, **4a** *vs* **4f**). Substrates bearing electron-donating groups on the aniline ring afforded the products **4g** and **4h** in 85 and 83% yields, respectively, whereas the electron-withdrawing nitro group failed to afford the desired product **4i.** The above observation could be explained on the basis of the nucleophilic behaviour of amino group. The presence of electron-donating groups (+ R effect) increases the nucleophilicity of the NH group, which facilitates the intramolecular attack, whereas in the case of **3i** the presence of the strong electron-withdrawing nitro group (–R effect) decreases the nuclophilicity as well as intramolecular attack. Substrate **3e** bearing acrylonitrile functionality provided the product **4e** in lower yields in comparison to acrylates (Scheme 4, **4a**–**d** *vs* **4e**).



[a]Inseparable complex mixture.

Scheme 4. Synthesis of pyrrolo[3,2-*c*]quinolines by intramolecular aza-Michael addition.

In summary, we have demonstrated an efficient and facile synthesis of pyrrolo[3,2-*c*]quinolines (core nucleus of natural product martinellic acid) via selective formation of pyrrole intermediate over indoles starting from easily accessible 2-(4-aminobut-1-yn-1-yl)anilines. The structures of intermediates and final products were confirmed by the x-ray crystallographic studies. The regioselectively cyclized product **5** embedded with an iodo handle could be used for further elaboration using palladium-catalyzed coupling reactions. From a synthetic point of view the developed strategy is simple, and general and can be used for the construction of variety of heterocyclic cores. Further investigations of developed chemistry are in progress and will be reported in due course.

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Notes and references

[a]*Organometallic Group, Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad-500007, India. plikhar@iict.res.in*

[b]*Department of Chemistry, University of Delhi, Delhi-110007, India. averma@acbr.du.ac.in*

[c]*X-Ray Crystallography Center, Indian Institute of Chemical Technology, Hyderabad-500007, India.*

† Electronic Supplementary Information (ESI) available: Datas and spectral Copies of ^{1}H, ^{13}C NMR and HRMS for target compounds. X-ray crystallograpic data of compounds **5a** and **4a**. See DOI: 10.1039/b000000x/

(1) (a) R. Noyori, ed. *Asymmetric Catalysis in Organic Synthesis*, Wiley: New York, 1994. (b) R. Noyori, T. Ohkuma, *Angew. Chem. Int. Ed.* 2001, **40**, 41; (c) K. Mikami, K. Wakabayashi, K. Aikawa, *Org. Lett.* 2006, **8**, 1517; (d) T. Ohkuma, N. Utsumi, M. Watanabe, K. Tsutsumi, N. Arai, Murata, K. *Org. Lett.* 2007, **9**, 2565; (e) T. Ohkuma, M. Koizumi, K. Muniz, G. Hilt, C. Kabuto, R. Noyori, *J. Am. Chem. Soc.* 2002, **124**, 6508; (f) H. Shimizu, D. Igarashi, W. Kuriyama, Y. Yusa, N. Sayo, T. Saito, *Org. Lett.* 2007, **9**, 1655; (g) R. J. Hamilton, S. H. Berger, *J. Am. Chem. Soc.* 2006, **128**, 13700.

(2) (a) P. Y. Ng, C. E. Masse, J. T. Shaw, *Org. Lett.* 2006, **8**, 3999; (b) D. A. Powell, R. A. Batey, *Org. Lett*. 2002, **4**, 2913; (c) B. B. Snider, Y. Ahn, S. M. O'Hare, *Org. Lett.* 2001, **3**, 4217; (d) D. Ma, C. Xia, J. Jiang, J. Zhang *Org. Lett.* 2001, **3**, 2189; (d) S. Comesse, M. Sanselme, A. Daich, *J. Org. Chem.* 2008, **73**, 5566; (e) Z. Zhang, Q. Zhang, Z. Yan, Q. Liu, *J. Org. Chem.* 2007, **72**, 9808; (f) D. Ma, C. Xia, J. Jiang, J. Zhang, W. Tang, *J. Org. Chem.* 2003, **68**, 442; (f) A. Shirai, O. Miyata, N. Tohnai, M. Miyata, D. J. Procter, D. Sucunza, T. Naito, *J. Org. Chem.* 2008, **73**, 4464; (g) K. E. Frank, J. Aubé, *J. Org. Chem.* 2000, **65**, 655.

(3) (a) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro, *Synlett.* 1999, 1432; (b) A. Arcadi, S. Cacchi, S. Di Giuseppe, G. Fabrizi, F. Marinelli, *Org. Lett.* 2002, **4**, 2409; (c) G. M. M. El-Taeb, A. B. Evans, S. Jones, D. W. Knight, *Tetrahedron Lett.* 2001, **42**, 5945; (d) S. P. Bew, D. W. Knight, *Chem. Commun.* 1996, 1007; (e) C. Schultz-Fademrecht, M. Zimmermann, R. Fro¨hlich, D. Hoppe, *Synlett* 2003, 1969; (f) Nichols, C. J.; J. J. Parks, Undergrad. *Chem. Res.* 2002, **1**, 2732; (g) D. W. Knight, *Electrophile-Induced 5-Endo Cyclizations.* In *Progress in Heterocyclic Chemistry*; G. W. Gribble, T. L. Gilchrist, Eds.; Pergamon Press: Oxford, 2002, **14**, 19; (h) B. Godoi , R. F. Schumacher, G. Zeni, *Chem. Rev.* 2011, **111**, 2937; (i) B. Singh, A. Chandra, S. Singh, R. M. Singh, *Tetrahedron* 2011, **67**, 505.

(4) (a) S. Roy, P. A. Covert, W. R. FitzGerald, D. K. Hore, *Chem. Rev.* 2014, DOI:10.1021/cr400418b; (b) S. Antoniotti, E. Dunach, *Tetrahedron Lett.* 2002, **43**, 3971; (c) R. Dua, S. Shrivastava, S. K. Sonwane, S. K. Srivastava, *Adv. Biol. Res.* 2011, **5**, 120; (d) C. Gil, S. Bräse, *J. Comb. Chem.* 2009, **11**, 175; (e) K. Bhadra, S. Kumar, *Med. Res. Rev.* 2011, **31**, 821; (f) H. Fan, J. Peng, M. T. Hamann, J. –F. Hu, *Chem. Rev.* 2008, **108**, 264; (g) G. Vincent, R. M. Williams, *Angew. Chem. Int. Ed.* 2007, **46**, 1517; (h) K. W. Bentley, Nat. Prod. Rep. 2006, **23**, 444; (i) P. L. McGrane, T. Livinghouse, *J. Am. Chem. Soc.* 1993, **115**, 11485; (j) J. C. Kwan, R. Ratnayake, K. A. Abboud, V. J. Paul, H. Luesch, *J. Org. Chem.* 2010, **75**, 8012; (k) M. S. Subhas, S. Racharlawar, B. Sridhar, P. K. Kennady, P. R. Likhar, M. L. Kantam, S. K. Bhargava, *Org. Biomol. Chem.* 2010, **8**, 3001; (l) P. R. Likhar, M. S. Subhas, S. Roy, M. L. Kantam, B. Sridhar, K. V. Mohan, B. Jagadeesh, *Organometallics* 2009, **28**, 3966; (m) M. V. Karkhelikar, S. Racharlawar, M. S. Subhas, B. Sridhar, P. R. Likhar, *J. Organomet. Chem*. 2012, **706**, 128.

(5) B. V. S. Reddy, M. Swain, S. M. Reddy, J. S. Yadav, B. Sridhar, *J. Org. Chem.* 2012, **77**, 11355.

(6) (a) K. J. Rossiter, Chem. Rev. 1996, **96**, 3201; (b) M. Boelens, *Perfum. Flavor* 1993, **18**, 2.

(7) (a) P. R. Likhar, M. S. Subhas, S. Roy, M. L. Kantam, B. Sridhar, R. K. Seth, S. Biswas, *Org. Biomol. Chem.* 2009, **7**, 85; (b) P. R. Likhar, S. S. Racharlawar, M. V. Karkhelikar, M. S. Subhas, *Synthesis* 2011, 2407; (c) R. R. Jha, R. K. Saunthwal, A. K. Verma, *Org. Biomol. Chem.* 2014, **12**, 552; (d) A. K. Verma, R. R. Jha, R. Chaudhary, R. K. Tiwari, S. K. R. Kotla, A. K. Danodia, *J. Org. Chem.* 2012, **77**, 8191.

(8) T. Okitsu, S. Yumitate, K. Sato, Y. In, A. Wada, *Chem. Eur. J.* 2013, **19**, 4992.

(9) (a) A. K. Verma, T. Aggarwal, V. Rustagi, R. C. Larock, Chem. Commun. 2010, **46**, 4064;

(10) See Supporting Information.