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PII: S0040-4039(18)31365-0
DOI: https://doi.org/10.1016/j.tetlet.2018.11.037
Reference: TETL 50422

To appear in: *Tetrahedron Letters*

Received Date: 25 October 2018
Revised Date: 11 November 2018
Accepted Date: 12 November 2018

Please cite this article as: Sujeevan Reddy, G., Babu Nallapati, S., Sri Saranya, P.S.V.K., Sridhar, B., Bhat Giliyaru, V., Chandrashekhar Hariharapura, R., Gautham Shenoy, G., Pal, M., Propargylamine (secondary) as a building block in indole synthesis involving ultrasound assisted Pd/Cu-catalyzed coupling-cyclization method: unexpected formation of (pyrazole)imine derivatives, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.11.037

Graphical Abstract

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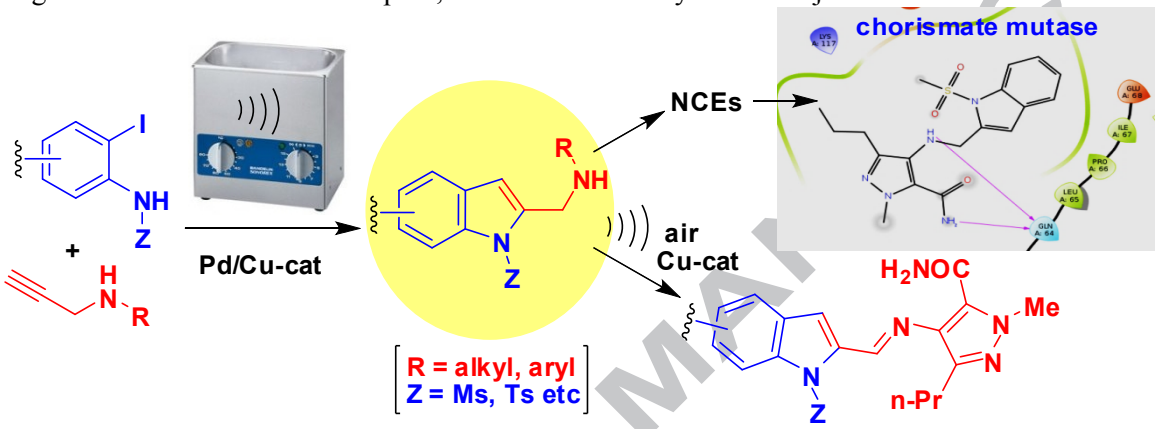

The rare use of propargylamine has been explored as a building block in the Pd/Cu-catalyzed synthesis of indoles (and certain imines) under ultrasound.

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Propargylamine (secondary) as a building block in indole synthesis involving ultrasound assisted Pd/Cu-catalyzed coupling-cyclization method: unexpected formation of (pyrazole)imine derivatives

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Propargylamine
Indole
Pyrazole
Palladium
Antitubercular

ABSTRACT

Propargylamine (secondary) has been explored as a building block in synthesizing indoles via an ultrasound assisted Pd/Cu-catalyzed coupling-cyclization method. Indoles containing a pyrazole moiety at C-2 attached *via* the -CH_2NH- linker (designed as potential anti-tubercular agents) were synthesized first and then generality / scope of the methodology was expanded by synthesizing other indoles. Unexpected formation of imine side products in first cases helped in synthesizing related (pyrazole)imines via a Cu catalyzed ultrasound assisted aerobic oxidation of precursor amines.

Propargylamines are well known building blocks in the synthesis of diverse *N*-heteroarenes including indoles.[1] The transition metal mediated coupling / cyclization (performed either in the same pot[2,3] or separately[4]) on the other hand has become a common strategy for the synthesis of 2-substituted indoles.[5] The one-pot coupling-cyclization leading to indole derivatives typically involves *in situ* generation of 2-alkynylanilides followed by spontaneous cyclization in the same pot. The use of a wide variety of terminal alkynes that are key reactants in these reactions has been reported till date. While the use of propargyl alcohol, ether and their derivatives (**A**, Fig. 1) are also common in these one-pot reactions the use of propargylamines (**B-D**, Fig. 1) especially the primary and secondary types (**B** and **C**, Fig. 1) surprisingly remained underexplored for the synthesis of indoles. For example, the use of propargylamine of type **D** (Fig. 1) was explored by Wang *et al* in the synthesis of indoline derivatives[6] (Scheme 1a) that was speculated to involve an initial Pd-catalyzed Sonogashira coupling followed by several steps (involving indole cyclization, regio- and chemoselective *N*-1-acylation, and finally, a 1,4-Michael addition). Previously,

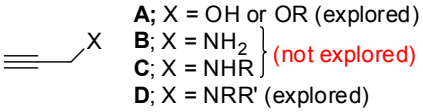

Fig. 1. Propargyl alcohol, ethers and amines explored/ not explored for indole synthesis.

one-pot Pd(II) catalyzed synthesis of cycloalkane-fused indoles was reported by Lu *et al*[7] (Scheme 1b) where **D** was used to prepare the required substrate. While the use of **C** under Sonogashira conditions has been reported by Larock *et al*[8] there is no precedence on the use of **B** or **C** for the direct and one-pot synthesis of indoles. Herein we report the use of propargylamine of type **C** for the synthesis of 2-substituted indoles *via* a one-pot, ultrasound assisted Pd/Cu-catalysed coupling-cyclization method (Scheme 1d). An unexpected formation of corresponding imine derivatives was also observed in certain cases during this study the details of which are presented.

Over the years compounds containing pyrazole framework have attracted particular interest because of their natural occurrences and diverse pharmacological properties including antimicrobial and antitubercular activities.[9] Indoles on the other hand are well known scaffolds for the design and synthesis of antimicrobial agents. In continuation of our effort in the discovery of indole-based novel inhibitors of chorismate mutase (CM) as potential antitubercular agents[10a,b] we became interested in constructing a

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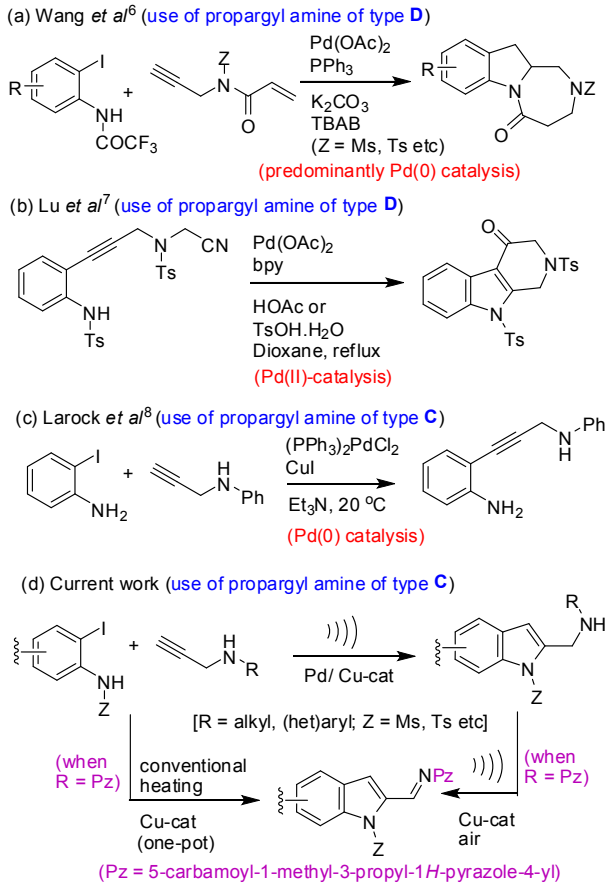


Scheme 1. Use of propargyl amines towards construction of indole ring

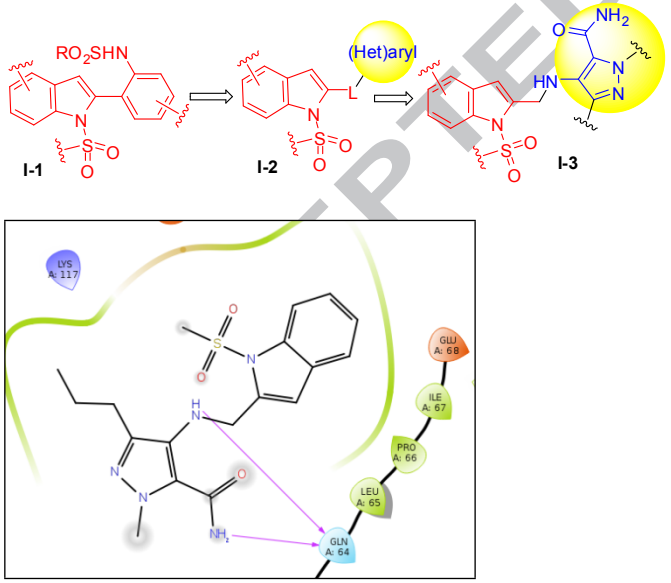
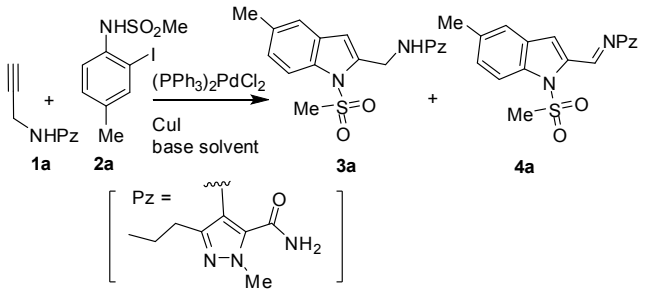


Fig. 2. Design of new indole derivative **I-2** and **I-3** from the known indole framework **I-1** and binding mode of **I-3** (a representative molecule) with chorismate mutase (PDB code: 2FP2).

library of molecules based on the framework **I-3** (Fig. 2) containing indole and pyrazole ring together. Our design mainly involved the introduction of a linker "L" at the C-2 of known indole[10c] **I-1** to provide structurally flexible and novel[10d] **I-2** possessing CM inhibiting properties. While a large variety of compounds can be derived from **I-2** by varying "L" and the "(het)aryl" group initially, we focused on the framework **I-3** (also derived from **I-2**) where the pyrazole[11] moiety as a representative heteroaryl group was connected to the indole ring *via* the -CH_2NH- linker. Indeed, this design i.e. introduction of linker and amide was justified by the *in silico* docking studies of a representative compound into the active site of CM (Fig 2) that indicated two H-bonds involving the linker and the amide –NH- of **I-3** with the GLN 64 residue of the protein. It was therefore necessary to have a direct and convenient access to compounds based on **I-3**.

Initially, the pyrazole-5-carboxamide derivative[12] **1a** and 2-iodoanilide **2a** were used as model substrates (Table 1) and the reaction was performed in the presence of $(PPh_3)_2PdCl_2$/CuI in EtOH at 80 ºC for 5 h when **3a** was isolated in moderate yield (entry 1, Table 1). Interestingly, a side product **4a** was isolated from the same reaction that was characterized as the corresponding imine derivative of **3a** (vide infra for further details). In order to suppress the formation of **4a** the reaction was performed in different solvents in the presence of different bases (entries 2-5, Table 1). However, no significant improvement was observed. Anticipating that **4a** was generated from **3a** we aimed for a shorter reaction time hoping that the conversion of **3a** to **4a** could be minimized. Accordingly, the reaction was performed at 60 °C under ultrasound irradiation using a laboratory ultrasonic bath producing irradiation of 35 kHz (entry 6, Table 1). To our delight the reaction was completed within 30 min affording **3a** in good yield with trace amount of **4a**. While formation of **4a** was suppressed completely in solvents like MeCN or DMSO the yield of **3a** was decreased significantly in these cases (entry 7 and 8). Notably, the use of CuI alone also afforded **3a** in good yield but the requirement of catalyst was higher and the reaction time was longer in this case (entry 9, Table 1). Overall, the combination of $(PPh_3)_2PdCl_2$-CuI-Et_3N-EtOH at 60 ºC under ultrasound irradiation was optimal for the preparation of **3a** and was used for the synthesis of various analogues of **3a**.

Table 1. Effect of reaction conditions on the coupling-cyclization of **1a** with **2a**



Entry	Base	Solvent	Temp (ºC); Time (h)	Yield (%)[b]	
				3a	**4a**
1	K_2CO_3	EtOH	80; 5	45	10
2	Cs_2CO_3	EtOH	80; 5	40	12
3	Et_3N	EtOH	80; 6	45	19
4	Et_3N	DMSO	80; 6	40	20
5	Et_3N	MeCN	80; 6	35	10
6	Et_3N	EtOH	60; 0.5	82[c]	5
7	Et_3N	MeCN	60; 0.5	52[c]	-
8	Et_3N	DMSO	60; 0.5	55[c]	-
9	Et_3N	EtOH	60; 2.5	80[c,d]	7

[a]Reactions were carried out using alkyne **1a** (1 mmol), **2a** (1.2 mmol), base (2.0 mmol), $(PPh_3)_2PdCl_2$ (1 mol%) and CuI (1 mol %) in a solvent (10 mL) under nitrogen.

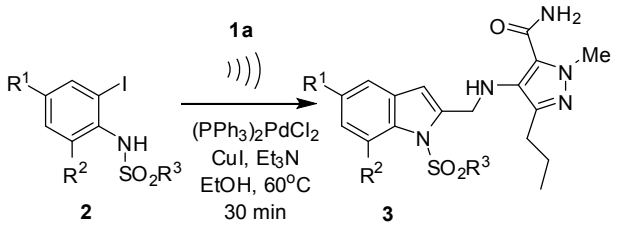
[b]Isolated yield.

[c]The reaction was performed under ultrasound.

[d]CuI (10 mol%) was used in place of $(PPh_3)_2PdCl_2$ (1 mol%) + CuI (1 mol %).

A variety of indole-pyrazole derivatives (**3**) were prepared *via* the coupling-cyclization of **1a** with a range of 2-iodoanilides (**2**) (Table 2). The ultrasound assisted reaction proceeded well in all these cases affording the desired product in good yields. Substituents like F, Cl, Br and Me on the anilide ring and groups such as mesyl, *p*-tosyl, benzenesufonyl and 2-thienosulfonyl at the anilide nitrogen were tolerated under the conditions employed. Notably, the use of a *bis*-propargylated amine (**1b**) under this reaction condition was also successful as **1b** participated in dual coupling-cyclization when reacted with **2c** affording an interesting *bis*-indole derivative **5** (Scheme 2).

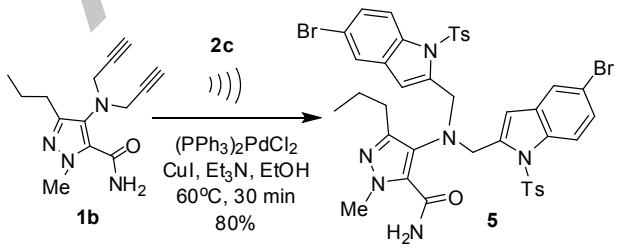
Table 2. Cu-catalysed synthesis of indole-pyrazole derivatives (**3**) under ultrasound irradiation.[a]



2-Iodoanilides (**2**)				Products (**3**)	%Yield[b]
	R^1	R^2	R^3		
2a	Me	H	Me	**3a**	82
2b	H	H	*p*-MeC_6H_4	**3b**	81
2c	Br	H	*p*-MeC_6H_4	**3c**	80
2d	Cl	H	2-thienyl	**3d**	74
2e	Cl	H	Ph	**3e**	73
2f	Br	H	2-thienyl	**3f**	75
2g	H	H	Me	**3g**	82
2h	Me	Me	Me	**3h**	70
2i	Cl	H	Me	**3i**	70
2j	Cl	H	*p*-MeC_6H_4	**3j**	74
2k	H	H	Ph	**3k**	73
2l	F	H	*p*-MeC_6H_4	**3l**	80

[a]Reactions were performed using a mixture of **1a** (1.0 mmol), **2** (1.2 mmol), $(PPh_3)_2PdCl_2$ (1 mol%), CuI (1 mol %) and Et_3N (2.0 mmol) in EtOH (10 mL) under ultrasound irradiation (35 KHz) at 60°C under nitrogen.

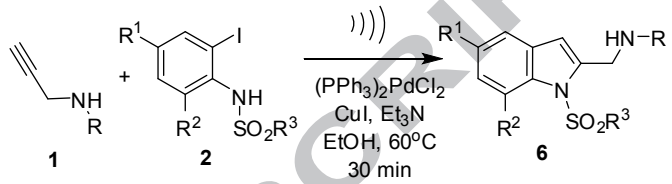
[b]Isolated yield.



Scheme 2. Ultrasound assisted coupling-cyclization of **1b** with **2c** under Pd/Cu-catalysis.

Having prepared a range of pyrazole containing novel indole derivatives (**3**) we focused on assessing generality of the present ultrasound assisted Pd/Cu-catalyzed reaction by using simpler propargylamines. Accordingly, **1c** (the benzene analogous to **1a**) were prepared and employed in Pd/Cu-catalyzed coupling-cyclization with a number of 2-iodoanilides (**2**) under ultrasound irradiation (Table 3) when the corresponding indoles (**6a-f**) were obtained in good yields. Indeed, propargylamines **1d** and **1e** also participated well and afforded the expected indole derivative **6g-i** in high yield (Table 3). While 2-(aminomethyl)indoles have been synthesized[13] via an elegant 3-component reaction (involving 2-ethynylanilides, paraformaldehyde and secondary amines in the presence of CuBr) the methodology appeared to be suitable for accessing indoles possessing a *tertiary* aminoethyl group rather than a secondary aminoethyl moiety (like **3** or **4**) at C-2.

Table 3. Use of propargylamine **1c-e** in indole synthesis.[a]



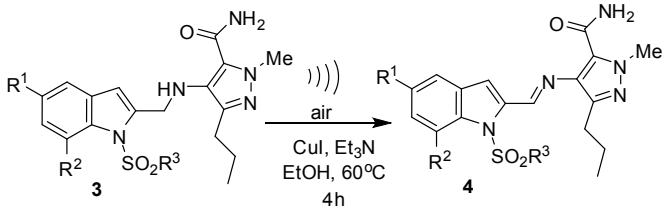
1	**2**	Products (**6**)				%yield[b]
R =		R^1	R	R^3		
1c; *o*-$(NH_2CO)C_6H_4$	**2b**	H	H	*p*-MeC_6H_4	**6a**	78
1c	**2c**	Br	H	*p*-MeC_6H_4	**6b**	80
1c	**2g**	H	H	Me	**6c**	82
1c	**2j**	Cl	H	*p*-MeC_6H_4	**6d**	77
1c	**2k**	H	H	Ph	**6e**	75
1c	**2l**	F	H	*p*-MeC_6H_4	**6f**	79
1d; Ph	**2b**	H	H	*p*-MeC_6H_4	**6g**	83
1e; Cyclohexyl	**2b**	H	H	*p*-MeC_6H_4	**6h**	80
1e	**2l**	F	H	*p*-MeC_6H_4	**6i**	82

[a]Reactions were performed using a mixture of **1c-e** (1.0 mmol), **2** (1.2 mmol), $(PPh_3)_2PdCl_2$ (1 mol%), CuI (1 mol %) and Et_3N (2.0 mmol) in EtOH (10 mL) under ultrasound irradiation (35 KHz) at 60 °C under nitrogen.

[b]Isolated yield.

Finally, the importance of imine compounds (Schiff bases) as antimicrobial agents[14] intrigued us to prepare **4a** (Table 1) and its analogues. Our initial attempt to synthesize **4a** as a sole or major product via the Cu-catalysed reaction of **1a** with **2a** in a single-pot under conventional heating was not successful. Indeed **4a** was isolated in ~ 40% yield when the reaction was performed for a longer time (24h). Considering **3a** as an *in situ* precursor of **4a**, we used **3a** as the substrate and the reaction was performed under ultrasound for 4h in the presence of air. To our satisfaction the yield of **4a** was improved significantly in this case (Table 4). Thus a number of imines (**4b-f**) were synthesized using this method in good yield (Table 4) whereas the one-pot method (i.e. the reaction of **1** with **2** for 24h) afforded these compounds in 35-58% yield. Notably all these reactions were performed using excess of Et_3N (5 mmol) as the conversion was slow when 2 mmol of Et_3N was used. The reaction was also sluggish in the absence of air or ultrasound and did not proceed in the absence of CuI indicating their key role in this transformation. Notably, our attempt to prepare the corresponding imine derivatives from indoles **6** was not successful under the condition employed. Perhaps the *N*-methylpyrazole moiety played a key role in oxidation of amine **3** to the imine **4** (see later for mechanistic discussion).

Table 4. Ultrasound assisted synthesis of imines (**4**).[a]



Amines (**3**)				Products (**4**)	%yield[b]
	R^1	R^2	R^3		
3a	Me	H	Me	**4a**	67
3b	H	H	*p*-MeC_6H_4	**4b**	65
3d	Cl	H	2-thienyl	**4c**	68
3j	Cl	H	*p*-MeC_6H_4	**4d**	69
3k	H	H	Ph	**4e**	70
3l	F	H	*p*-MeC_6H_4	**4f**	78

[a]Reactions were performed using a mixture of **3** (1.0 mmol), CuI (10 mole %) and Et_3N (5.0 mmol) in EtOH (10 mL) under ultrasound irradiation (35 KHz) at 60°C for 4h in the presence of air.

[b]Isolated yield.

All the compounds (**3-6**) synthesized were characterized by spectral data. Briefly, a singlet near ~6.3–6.7 δ and a doublet near 4.2 δ in the ^{1}H NMR spectra of **3** were due to the C-3 indole proton and the –CH_2NH- moiety, respectively. A similar ^{1}H NMR data were obtained for **6**. However, the compound **4** was characterized by presence of the imine proton near 9 δ in the ^{1}H NMR spectra. Nevertheless, the molecular structure of two representative compounds e.g. **3a** (amine) and **4b** (imine) was confirmed unambiguously by their respective single crystal X-ray data (Fig. 3 and 4).[15] The data suggested anti –CH=N- geometry for **4b** and an intramolecular H-bond between the imine nitrogen and the amidic hydrogen (Fig. 4).

According to a plausible mechanism[2,3] (Scheme 3) the initial step (Sonogashira coupling) involved the generation of organo-Pd(II) species **E-1** [via oxidative addition of Pd(0) to **2**] that on transmetalation with Cu(I)-acetylide (generated *in situ* from **1**) afforded **E-2**. On reductive elimination **E-2** produced **E-3** with the regeneration of Pd(0)-catalyst thereby completing the first catalytic cycle. Next, the Cu(I)-catalyst participated in the second catalytic cycle via promoting the intramolecular cyclization of **E-3**. Indeed, the interaction of Cu(I) with the alkyne moiety of **E-3** seemed to be favoured by the coordination with the proximate amino group leading to **E-4** followed by **E-5** that afforded the desired indole **3**. The regeneration of Cu(I)-catalyst completed the second catalytic cycle. In the absence of ultrasound the Cu-catalyst participated further to afford imine **4** as a side product (Table 1) via **E-6** (*path a*) though less efficiently perhaps due to the low conversion rate of Cu(0) generated to the Cu(I) species in the absence of a proper oxidizing agent. However, efficiency of this step was improved in the presence of aerial oxygen[16] when **E-6** was generated from **3** via *path b* (Table 4). Moreover, the formation of **E-6** appeared to be more facile in case of **3** over **6** perhaps due to the enhanced resonance stabilization caused by the *N*-methylpyrazole ring that was absent in case of **6** (Fig. 5). It is worthy to mention that while one or more steps of these catalytic cycles e.g. oxidative addition, trans-metalation, reductive elimination of Pd(0), or cyclization etc were accelerated by ultrasound, the ultrasound played an important role in driving the reaction towards completion within short duration.[17]

Most of the pyrazole containing compounds i.e. **3** and **4** were tested for their CM inhibitory properties *in vitro*[18] using an assay

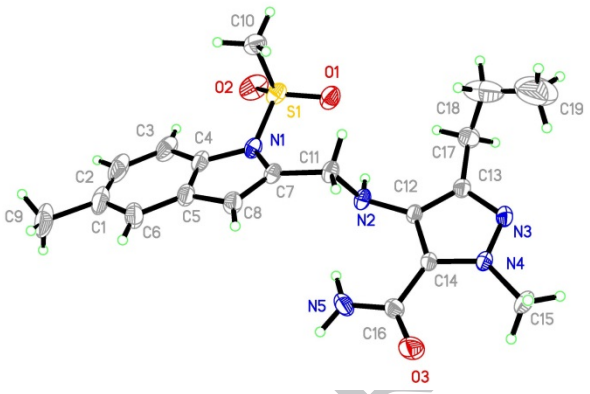


Fig. 3. A view of **3a**, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii.

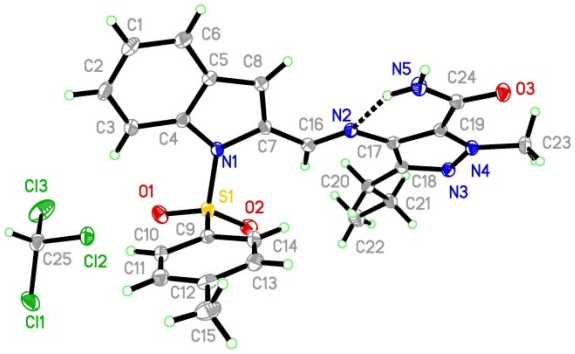
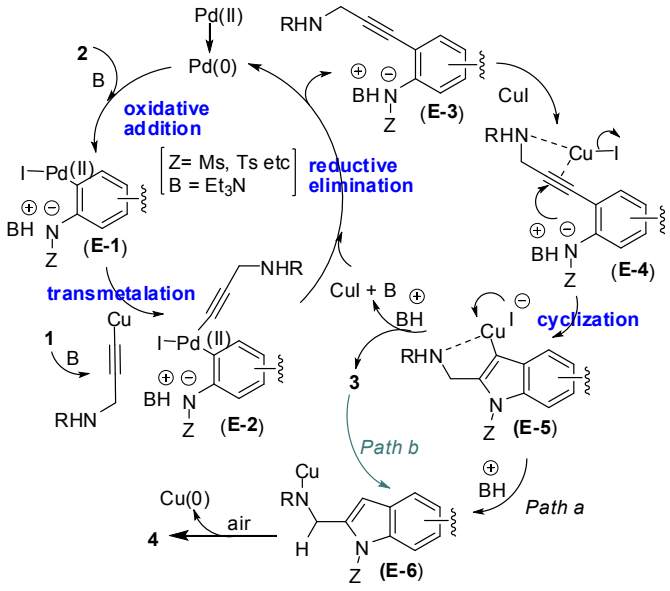


Fig. 4. A view of **4b**, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii. Intramolecular hydrogen bond is shown as dashed lines. Minor disordered atoms (ClD/Cl2D/Cl3D) of trichloromethane solvate have been omitted for clarity.



Scheme 3. The plausible reaction mechanism for ultrasound assisted Pd/Cu-catalysed coupling-cyclization of propargylamine (**1**) with 2-iodoanilides (**2**).

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that involved measurement of catalytic activity of enzyme (CM) in the conversion of chorismate (substrate) to prephenate. A known inhibitor i.e. 4-(3,5-dimethoxyphenethylamino)-3-nitro-5-sulfamoylbenzoic acid[19] was used as a reference compound (IC_{50} < 10 mM). The compound **3c** showed significant inhibition (57.4

± 3.70%) of CM when tested at 50 μM. This was supported by the initial docking of **3c** into the CM that showed H-bond between –$CONH_2$ group of **3c** with ILE 67 and TYR 110 residue of CM. While detailed pharmacological studies of this class of compounds are currently ongoing the compound **3c** appeared to be of further interest in view of the fact that tuberculosis is a leading cause of death worldwide.

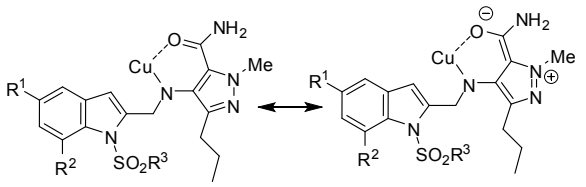

Fig. 5. Resonance stabilization of **E-6** generated from **3**.

In conclusion, we have described the rare use of propargylamine (secondary) as a building block in the synthesis of 2-substituted indoles. Accordingly, ultrasound assisted methodology has been developed to prepare (i) indoles via Pd/Cu-catalyzed coupling-cyclization strategy and (ii) certain imines via Cu-catalyzed aerobic oxidation of precursor amines. Initially indoles containing a pyrazole moiety at C-2 attached *via* the -CH_2NH- linker were synthesized that were originally designed as potential anti-tubercular agents. Thus 1-methyl-4-(prop-2-ynylamino)-3-propyl-1*H*-pyrazole-5-carboxamide was coupled for the first time with a variety of 2-iodoanilides to afford novel indoles in 70-82% yield. Subsequently, the scope and generality of this methodology was expanded by preparing similar but simpler indole derivatives in 75-83% yield. The unexpected formation of imine side products in certain cases helped in synthesizing related (pyrazole)imines in 65-78% yield. While this finding seemed to be uncommon the results however indicated that the imine formation was favored by the presence of *N*-methylpyrazole moiety. The initial chorismate mutase inhibitory properties of these indole derivatives highlighted their potential for further Med Chem effort. Overall, the current research related to propargylamine / indole chemistry could attract further interest.

Acknowledgements

GSR thanks DST, India for a INSPIRE fellowship (IF160590). Authors thank the Management of DRILS, Hyderabad, India and Manipal University, Manipal, India for encouragement and support and DBT, New Delhi, India for financial assistance (Grant No. BT/PR12817/COE/34/23/2015). Authors also thank Prof P. Misra and Ms. R. Edwin of DRILS, Hyderabad for *in vitro* assay.

Supplementary data

Supplementary data associated with this article can be found, in the on line version, at xxxxxxxxx

References and notes

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Highlights

- Explored the rare use of propargylamine as a building block in the Pd/Cu catalyzed synthesis of indoles under ultrasound.
- Indoles containing a pyrazole moiety at C-2 attached *via* the -CH_2NH- linker were synthesized as anti-tubercular agents.
- Synthesized related (pyrazole)imines via a Cu catalyzed ultrasound assisted aerobic oxidation of precursor amines.