RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 24001

Received 1st April 2014
Accepted 22nd May 2014

DOI: 10.1039/c4ra02865a

www.rsc.org/advances

Microwave-assisted palladium mediated efficient synthesis of pyrazolo[3,4-*b*]pyridines, pyrazolo-[3,4-*b*]quinolines, pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]quinazolines†

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An efficient method was developed for the synthesis of pyrazole fused heterocycles *via* the palladium-catalyzed solvent free reaction of β-halovinyl/aryl aldehydes and 3-aminopyrazoles/5-aminopyrazoles under microwave irradiation in good yields. This method is applicable for the efficient synthesis of a wide range of substituted pyrazolo[3,4-*b*]pyridines, pyrazolo[3,4-*b*]quinolines, pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]quinazolines. Four of the synthesized pyrazole fused compounds showed *in vitro* cytotoxic activities almost comparable to the drug doxorubicin against the cervical HeLa cancer cell line and prostate DU 205 cancer cell line.

Introduction

Pyrazole fused heterocycles such as pyrazolo[3,4-*b*]pyridine, pyrazolo[3,4-*b*]quinoline, pyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*a*]quinazoline are found as building blocks of different pharmaceutically important heterocyclic compounds and they possess a wide range of biological activities.[1–4] Fig. 1 shows some of the biologically important pyrazole fused heterocycles. Pyrazolo[3,4-*b*]pyridine derivative **I** (BAY 41-2272) stimulates soluble guanylate cyclase (sGC) and induces vasodilation,[5] 6-aryl pyrazolo[3,4-*b*]pyridine **II** is reported as potent inhibitor of glycogen synthase kinase-3 (GSK-3),[6] cyclopentapyrazolo[1,5-*a*]pyrimidine (**III**) is a 5-HT$_6$ receptor antagonist with K_i < 1 nM,[7] compound **IV** (Zaleplon) is a known drug for the treatment of sleep disorder[8] and cyclopentane ring fused pyrazolo[1,5-*a*]pyrimidine **V** has the highest affinity (K_i = 88 pM) to the 5-HT$_6$ receptor.[9] The importance of these pyrazole fused heterocycles has led to the development of new procedures for the synthesis of these targets.[1–4] For example, recently, Park S. B. and coworkers reported an acid catalyzed synthetic method for pyrazolo[3,4-*b*]pyridines using indole-3-carboxaldehyde derivatives and aminopyrazoles as the starting materials.[1a] Acid catalyzed syntheses of pyrazolo[3,4-*b*]pyridines, pyrazolo[3,4-*b*]-quinolines and pyrazolo[1,5-a]pyrimidines under microwave irradiation are also reported in the literature.[1d,2f,3b] Very recently, Batra S. and coworkers reported one Pd catalyzed synthesis of similar type of pyrazolopyridines using potassium 2-amino-(hetero)benzoates and 2-haloarylaldehydes as the starting materials.[1i] In spite of the presence of these synthetic methods for the synthesis of pyrazole fused compounds with different substituted patterns, there is still lack of environmentally benign general method for the synthesis of all of these important fused heterocycles.

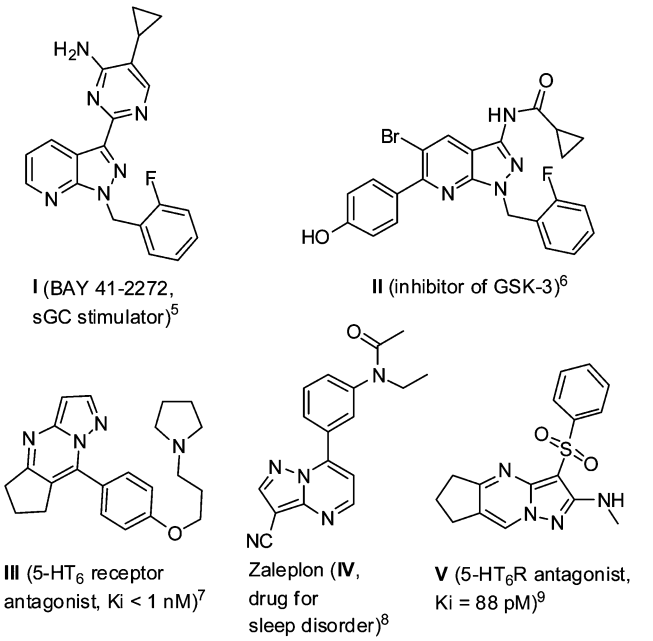

Fig. 1 Examples of bioactive pyrazolo[3,4-*b*]pyridines and pyrazolo-[1,5-*a*]pyrimidines.

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† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR spectra of compounds **3a–p**, **6a–l** and MTT assay protocol. See DOI: 10.1039/c4ra02865a

Microwave heating to perform a chemical reaction is becoming popular nowadays due to the decreased reaction time, high and cleaner yield of products and enhancement of the chemo-, regio- and stereoselectivity of the reactions. Again, microwave heating has been used to perform several novel reactions using transition-metals as the catalysts.[10]

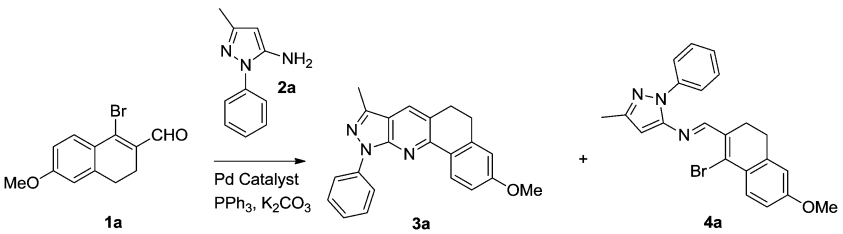
In view of the occurrence of these pyrazolo[3,4-*b*]pyridine, pyrazolo[3,4-*b*]quinoline pyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*a*]quinazoline moieties in biologically active molecules, as well as our interest in the synthesis of novel heterocycles[11] we sought to develop an efficient method for the synthesis of all of these classes of compounds using readily available starting materials. Herein, we report an efficient Pd catalyzed synthesis of these important pyrazole fused heterocycles using β-halovinyl/aryl aldehydes and 3-aminopyrazoles/5-aminopyrazoles as the starting materials under microwave irradiation in solvent-free condition.

Results and discussion

We started our work by examining the reaction of β-bromovinyl aldehyde **1a** (1.0 mmol) with equimolar amount of 5-aminopyrazole **2a** (1.2 mmol) in presence of Pd catalyst (Table 1). At the beginning, we observed that a catalytic amount (2.5 mol%) of $PdCl_2$ along with triphenylphosphine (5 mol%) as a ligand furnished compound **3a** in 15% yield under thermal condition in 24 hours using DMF as the solvent (entry 1, Table 1). Compound **3a** was fully characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The ^{1}H NMR spectrum of compound **3a** exhibited a characteristic aromatic singlet signal at δ 7.70 for the pyrazolo[3,4-*b*]pyridine ring proton. This ^{1}H NMR spectrum also showed a doublet signal at δ 8.43 (J = 7.6 Hz, 2H), two triplet signals at δ 7.52 (J = 7.4 Hz, 2H) and 7.23 (J = 5.1 Hz, 1H), because of the phenyl group attached to nitrogen atom of pyrazolo[3,4-*b*]pyridine. Moreover, the ^{1}H NMR of this compound showed two doublet signals at δ 8.38 (J = 8.7 Hz, 1H), 6.75 (J = 2.5 Hz, 1H) and one double doublet signal at δ 6.93 (J = 8.6 Hz & 2.6 Hz, 1H) for the protons of dihydronaphthalene ring. The ^{13}C NMR spectrum of **3a** showed twenty one signals. The EI mass spectra of compound **3a** exhibited molecular ion peaks at m/z 341.2. After confirming the structure of **3a** we tried the same reaction of **1a** and **2a** using 2.5 mol% of $Pd(OAc)_2$ as the catalyst in DMF which provided slightly improved yield of compound **3a** (22%, entry 2, Table 1). Use of solvent DMSO in place of DMF in this reaction diminished the yield of **3a** (15%, entry 3, Table 1). Then, we examined the influence of microwave (MW) irradiation (700 W, 120 °C, 14 bar) on the reaction of **1a** and **2a** in presence of 2.5 mol% $Pd(OAc)_2$ catalyst in DMF.

Gratifyingly, under this condition substantial increase in yield of **3a** to 68% along with a significant reduction in reaction time from 24 hours to 15 minutes was observed (entry 4, Table 1). Interestingly, when we performed the reaction in neat condition, we observed further increase in yield of **3a** to 81% (entry 5, Table 1) under microwave irradiation. The enhancement of reaction rate under solvent-free condition was quite encouraging due to the different advantages of solvent-free reactions.[12] To explore the effect of catalyst loading, when the quantity of the loaded catalyst was increased to 5 mol% under solvent free condition, there was no improvement in the yield of the product **3a** (entry 6, Table 1). But when the catalyst loading

Table 1 Optimization of the reaction conditions for the synthesis of **3a**[a]

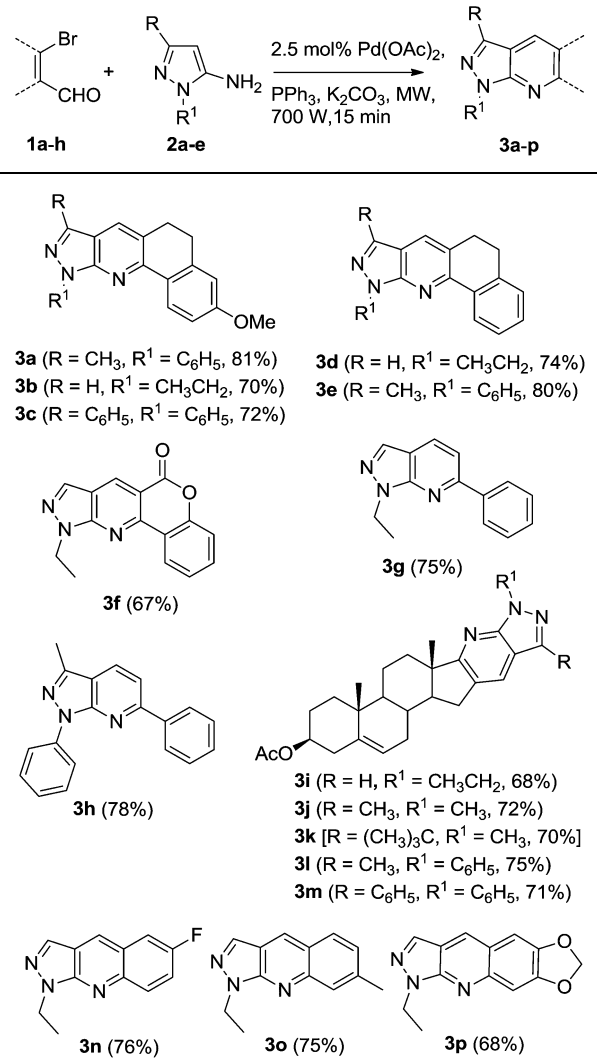


					%Yield[b]	
Entry	Pd source (mol%)	Solvent	Thermal/MW	Time	**3a**	**4a**
1	$PdCl_2$ (2.5)	DMF	120 °C	24 h	15	72
2	$Pd(OAc)_2$ (2.5)	DMF	120 °C	24 h	22	65
3	$Pd(OAc)_2$ (2.5)	DMSO	120 °C	24 h	15	64
4	$Pd(OAc)_2$ (2.5)	DMF	MW (700 W)	15 min	68	18
5	$Pd(OAc)_2$ (2.5)	Neat	MW (700 W)	15 min	81	7
6	$Pd(OAc)_2$ (5)	Neat	MW (700 W)	15 min	80	8
7	$Pd(OAc)_2$ (1.5)	Neat	MW (700 W)	15 min	64	14
8	$PdCl_2(PPh_3)_2$ (2.5)	Neat	MW (700 W)	15 min	45	38
9	—	Neat	MW (700 W)	15 min	0	83
10	$Pd(OAc)_2$ (2.5)	Neat	MW (500 W)	15 min	52	24
11	$Pd(OAc)_2$ (2.5)	Neat	MW (800 W)	15 min	77	4

[a] All reactions were performed in presence of PPh_3 (5 mol%) and K_2CO_3 (2.1 mmol). [b] Isolated yield.

was decreased to 1.5 mol%, we observed the decreased yield of **3a** (64%) under solvent free condition (entry 7, Table 1). Moreover, the yield of desired product **3a** decreased to 45% when $PdCl_2(PPh_3)_2$ was used as the catalyst (entry 8, Table 1). Our attempt to perform the reaction without catalyst furnished only the imine derivative **4a** under the solvent free condition (entry 9, Table 1). Then, we looked at the effect of microwave power on the yield of compound **3a** and we noticed that use of 500 Watt MW power decreased the yield of **3a** to 52% (entry 10, Table 1). The use of 800 Watt MW power also afforded slightly less yield (77%) of compound **3a** (entry 11, Table 1). In all the above reaction conditions the reaction of β-bromovinyl aldehyde **1a** and 5-aminopyrazole **2a** afforded the imine derivative **4a** as a byproduct with different yields which are shown in Table 1.

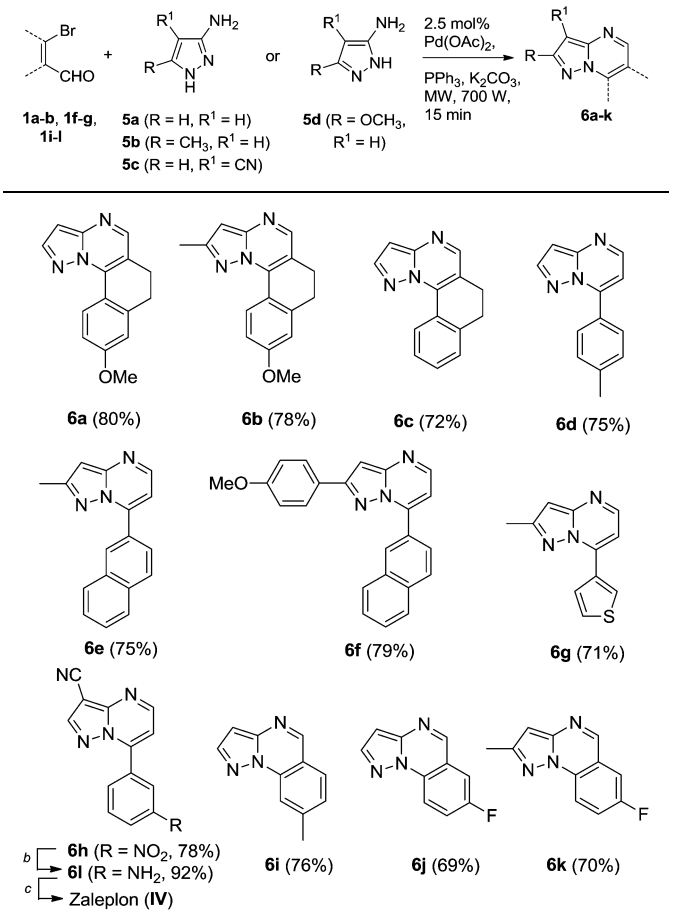
Table 2 Palladium catalyzed synthesis of pyrazolo[3,4-*b*]pyridines (**3a–m**) and pyrazolo[3,4-*b*]quinolines (**3n–p**)[a]



[a] A grinded mixture of β-halo aldehyde (1.0 mmol), 5-aminopyrazole (1.2 mmol), $Pd(OAc)_2$ (2.5 mol%), PPh_3 (5 mol%) and K_2CO_3 (2.1 mmol) was irradiated in a closed vessel in a Synthos 3000 microwave reactor at 700 Watt (120 °C and 14 bar) for 15 minutes.

Using the optimized reaction condition (entry 5, Table 1), we evaluated the scope of the reaction by using different β-halovinyl/aryl aldehydes **1a–i** and 5-aminopyrazoles **2a–e** (Table 2). The reactions of different cyclic β-bromovinyl aldehydes and β-bromovinyl-β-phenyl aldehydes with a range of 1-substituted-5-aminopyrazoles under the optimized reaction condition afforded pyrazolo[3,4-*b*]pyridines **3b–h** in 67–80% yields. Similarly, the reaction of steroidal β-bromovinyl aldehyde with different 1-substituted-5-aminopyrazoles afforded an array of steroidal pyrazolo[3,4-*b*]pyridines **3i–m** in 68–75% yields. These steroids bearing heterocycles are very important compounds due to their remarkable biological activities and in last few decades enormous efforts are being made to annelate steroidal moiety with different heterocycles.[13] In addition to β-bromovinyl aldehydes, we performed the reaction of 2-bromobenzaldehyde derivatives having electron donating/withdrawing groups with 1-substituted-5-aminopyrazoles under the optimized condition to provide the pyrazolo[3,4-*b*]quinolines **3n–p** in 68–76% yields.

Table 3 Palladium catalyzed synthesis of pyrazolo[1,5-*a*]pyrimidines (**6a–h**) and pyrazolo[1,5-*a*]quinazolines (**6i–k**)[a]



[a] A grinded mixture of β-halo aldehyde (1.0 mmol), 3-aminopyrazole/5-aminopyrazole (1.0 mmol), $Pd(OAc)_2$ (2.5 mol%), PPh_3 (5 mol%) and K_2CO_3 (2.1 mmol) was irradiated in a closed vessel in a Synthos 3000 microwave reactor at 700 Watt (120 °C and 14 bar) for 15 minutes. [b] H_2 (ballon pressure), Pd/C, EtOH, rt, 2 h. [c] Ref. 14b.

Table 4 IC_{50} values of compounds **3a–p** and **6a–l** determined by MTT assay

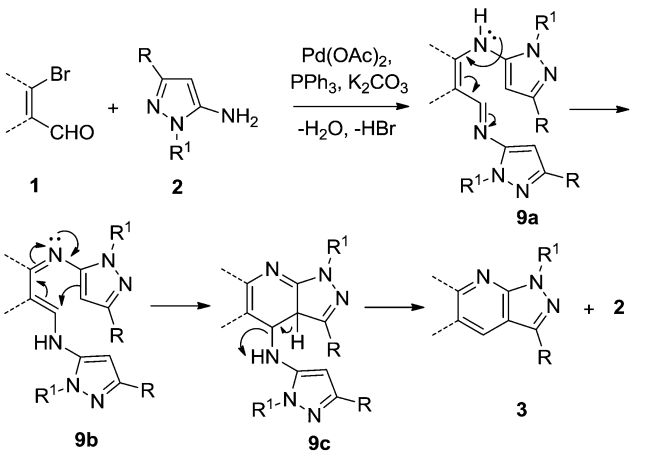
Compound	IC_{50} at 10 μM (HeLa)	IC_{50} at 10 μM (DU-145)
3a–g, 3i–o	>100	>100
3h	12.60 ± 0.2021	10.37 ± 0.219
3p	11.34 ± 0.1098	10.09 ± 0.277
6a	13.34 ± 0.0604	9.75 ± 0.156
6d	10.41 ± 0.2175	10.77 ± 0.124
6b–c, 6e–l	>100	>100
Doxorubicin	9.76 ± 0.1141	9.00 ± 0.721

The formation of isomer **3** was proved by comparison of new spectral and physical data with those reported in the literature for compound **3e**.[14c]

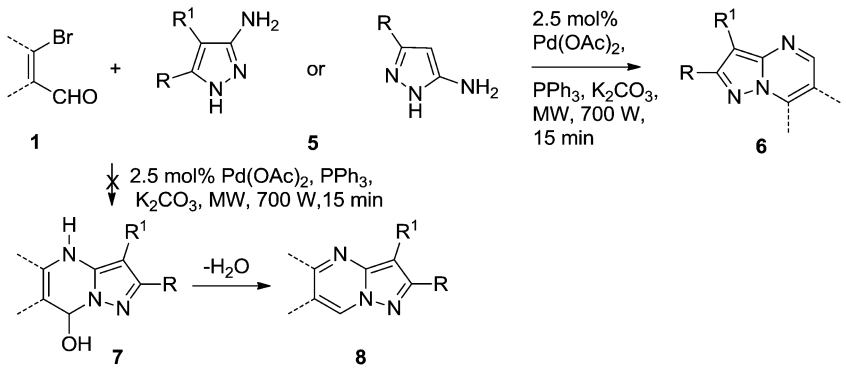
Next, we shifted our focus on the synthesis of pyrazolo[1,5-*a*]-pyrimidines. It was interesting to find that the reaction of β-halovinyl aldehyde **1a** and 3-aminopyrazole (**5a**) under the above optimized condition was very regioselective and it afforded 80% yield of pyrazolo[1,5-*a*]pyrimidine **6a** (Table 3). Encouraged by this result, we tried to extend this reaction to some other β-bromovinyl aldehydes with different 3-aminopyrazoles/5-aminopyrazole having free N–H group to furnish pyrazolo[1,5-*a*]pyrimidines **6b–h** in 71–79% yield. The formation of pyrazolo[1,5-*a*]pyrimidine was proved by ^{1}H NMR, ^{13}C NMR and mass spectra. Although there was also the possibility of the formation of regio isomer **8** as shown in Scheme 1, *via* coupling reaction of the vinylic amino group of **5** with the vinyl bromide group of **1**, followed by elimination of a water molecule, it is worth noting that only isomer **6** was formed under this microwave condition. The formation of isomer **6** was proved by comparison of new spectral and physical data with those reported in the literature for compounds **6c** and **6h**.[14a,b] To see the feasibility of the reaction for the synthesis of pyrazolo[1,5-*a*]-quinazoline derivatives, β-bromoaryl aldehydes (**1f–g**) were treated with 3-aminopyrazoles **5a–b** under similar reaction conditions which afforded the desired pyrazolo[1,5-*a*]quinazolines **6i–k** in 69–76% yields. In all the reactions good functional group compatibility was demonstrated with β-bromovinyl aldehydes substituted with methoxy/methyl/nitro phenyl rings. Although metal catalyzed reactions in presence of multiple heteroatoms are usually challenging owing to their tendency to form metal–heteroatom complexes, all the above reactions were very effective to provide pyrazole derivatives.[15] The starting β-bromovinyl aldehydes (**1a–e**, **1i–l**) were synthesized easily by following known procedure.[16] The nitro group in compound **6h** was hydrogenated easily to provide the pyrazolo[1,5-*a*]pyrimidine **6l**.[14b] Our attempt to scale up the compound **6h** in four gram scale also afforded 77% yield of **6h** from its corresponding starting β-bromovinyl aldehyde **1l** under the optimized condition.

All the synthesized compounds (**3a–p**, **6a–l**) were screened *in vitro* for cytotoxic activities against cervical HeLa cancer cell line and prostate DU 205 cancer cell line using MTT-micro cultured tetrazolium assay[17] and drug doxorubicin as a positive control. Compounds **3h**, **3p**, **6a** and **6d** showed *in vitro* cytotoxic activities almost comparable to the drug doxorubicin against cervical (Table 4).

The formation of the pyrazolo[3,4-*b*]pyridine **3** is envisaged to occur *via* a mechanism which is shown in Scheme 2. Previously we found that in absence of Pd catalyst the reaction of β-bromoaryl aldehyde **1a** with 5-aminopyrazole **2a** afforded only the imine derivative **4a** as shown in Table 1. In presence of Pd catalyst, the Buchwald–Hartwig cross coupling reaction,[18] and



Scheme 2 Proposed mechanism for the formation of **3**.



Scheme 1 Synthesis of pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]quinazolines.

imine formation reaction of the β-bromovinyl/aryl aldehyde **1** with 5-aminopyrazole **2** generates probably enaminoimine **9a**, which on rearrangement gives azadiene intermediate **9b** (Scheme 2). Then a six-electron cyclization of **9b** affords final compound **3** with the loss of one molecule of 5-aminopyrazole **2** *via* intermediate **9c**. Our attempt to perform the reaction between **2a** and **4a** also afforded compound **3a**, which also supported our proposed mechanism. Although, there are few references for the direct C-3 and C-4 alkylations of pyrazole moiety by metal catalyst,[19,1i] to the best of our knowledge this is the first example of C-4 alkylation of pyrazole *via* cascade imination/coupling/cycloaddition which leads to the formation pyrazolo[3,4-*b*]pyridine. On the other hand, the formation of the product **6** is envisaged to occur *via* imine formation between aldehyde group of **1** with free amine group of pyrazole **5**, followed by N–H tautomerization (in case of 3-aminopyrazoles, **5a–c**) and Buckwald–Hartwig cross coupling reaction.

Conclusions

In conclusion, we have developed an environmentally friendly general procedure for the efficient and fast synthesis of biologically important pyrazole fused heterocycles pyrazolo[3,4-*b*]-pyridines, pyrazolo[3,4-*b*]quinolines, pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]quinazolines. A wide range of β-halovinyl/aryl aldehydes undergo this reaction with N-substituted 5-aminopyrazoles and N–H free 3-aminopyrazoles/5-aminopyrazoles in presence of palladium catalyst (2.5 mol%) under microwave irradiation. The general applicability for the synthesis of all four important heterocycles, simplicity in operation, solvent-free synthesis, energy efficiency (shorter reaction time under microwave irradiation), very less catalyst loading and good yields of products make this procedure greener and more cost-effective. Preliminary *in vitro* cytotoxic studies showed that compounds **3h**, **3p**, **6a** and **6d** have cytotoxic activities almost comparable to the drug doxorubicin against cervical HeLa cancer cell line and prostate DU 205 cancer cell line.

Acknowledgements

Kommuri Shekarrao thanks CSIR, New Delhi for the award of Senior Research Fellowship (CSIR-SRF). We are grateful to Director, CSIR-NEIST for his keen interests. We gratefully acknowledge financial support from CSIR-ORIGIN (CSC0108), CSIR-ACT (CSC0301) and CSIR-INSPIRE (CSC0107) projects.

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