ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 7779–7781

www.rsc.org/chemcomm

COMMUNICATION

Pd-mediated new synthesis of pyrroles: their evaluation as potential inhibitors of phosphodiesterase 4†

G. Rajeshwar Reddy,[ab] T. Ram Reddy,[a] Suju C. Joseph,[a] K. Sateesh Reddy,[a] L. Srinivasula Reddy,[a] P. Mahesh Kumar,[a] G. Rama Krishna,[c] C. Malla Reddy,[c] D. Rambabu,[d] Ravikumar Kapavarapu,[d] Chandana Lakshmi,[d] Teja Meda,[d] K. Krishna Priya,[d] Kishore V. L. Parsa[d] and Manojit Pal*[d]

Received 21st April 2011, Accepted 17th May 2011
DOI: 10.1039/c1cc12321a

A sequential Pd-mediated multi-component reaction followed by Suzuki or Heck or Sonogashira coupling in a single pot has been developed for the synthesis of functionalized pyrroles as potential inhibitors of PDE4.

Pyrrole derivatives have attracted particular attention in the area of drug discovery.[1] For example, anticancer drug candidate tallimustine and blockbuster cholesterol lowering agent atorvastatin (or lipitor) belong to this class. The classical methods for the synthesis of pyrroles *e.g.* Hantzsch,[2] Knorr,[3] and Paal–Knorr[4] reactions though effective suffer from several drawbacks. Recently, multi-component reactions (MCRs) have found wide applications in the synthesis of pyrroles.[5] MCRs not only allow union of three or more starting materials in a single synthetic operation with high atom economy and bond-forming efficiency, but also avoid isolation and purification of any intermediates thereby minimizing waste, labor, and cost.[6] Thus, synthesis of functionalized pyrroles has been reported *via* an Fe(III)-catalyzed four-component coupling reaction of 1,3-dicarbonyl compounds, amines, aldehydes, and nitroalkanes.[7] More recently, we have observed that Pd-mediated[8] MCR provides a more versatile and direct route to functionalized pyrroles of potential medicinal value.

The phosphodiesterase 4 (PDE4) inhibitors are known to be beneficial for the potential treatment of asthma and chronic obstructive pulmonary disease (COPD).[9] The existing therapies *e.g.* steroids, β2 agonists and antimuscarinics[10] are effective but do not address the long-term decline of lung function, the hallmark of COPD. PDE4 inhibitors exert anti-inflammatory and bronchodilatory effects *via* elevation of the c-AMP level and therefore have potential to provide relief of symptoms, prevent complications and/or progression of these diseases. Indeed, the most advanced PDE4 inhibitors *e.g.* cilomilast and roflumilast have shown promising results in Phase III clinical trials. As part of our ongoing effort on the identification of novel inhibitors of PDE4 we report the evaluation of a series of pyrroles (**C**, Fig. 1) designed from the known inhibitors **A**[11a] and **B**.[11b] The synthesis and functionalization of **C** was carried out using a Pd-based new MCR in a single pot.

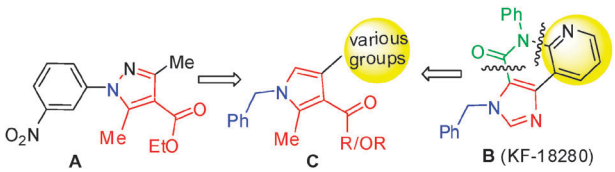


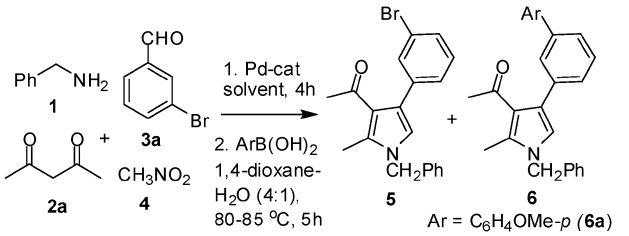
Fig. 1 Design of pyrrole based novel inhibitors (**C**) of PDE4.

To synthesize **C** in a single pot we examined the reaction of 3-bromobenzaldehyde (**3a**), benzylamine (**1**), acetyl acetone (**2a**) and nitromethane (**4**) in the presence of a Pd catalyst. Our goal was to identify a suitable Pd catalyst that would allow further functionalization *via* other key Pd-catalyzed reactions such as Suzuki, Sonogashira, Heck, *etc.* Accordingly, $PdCl_2$ was chosen as an initial catalyst for four component reactions (step 1) followed by Suzuki coupling (step 2) using 4-methoxyphenyl boronic acid in the same pot (Table 1). No product was formed when the reaction was performed at room temperature using DMF as a solvent in the first step (entry 1, Table 1). Increase in reaction temperature to 80–85 °C afforded the desired product **6a** along with **5** (entry 2, Table 1). Changing the solvent from DMF to 1,4-dioxane did not improve the yield of **6a** (entry 3, Table 1). However, the use of additional Pd-catalyst in step 2 especially $(PPh_3)_2PdCl_2$ improved the yield of **6a** significantly (entry 4, Table 1). Moreover, conducting step 1 in the absence of the solvent was found to be beneficial (entry 5, Table 1). Based on these observations we replaced $PdCl_2$ by $(PPh_3)_2PdCl_2$ (entry 6, Table 1). The step 1 was performed under neat conditions and no additional catalyst was used in step 2. The reaction proceeded well affording **6a** in 85% yield. The MCR did not proceed in the absence of a Pd catalyst (entry 7, Table 1).

[a] *Custom Pharmaceutical Services, Dr. Reddy's Laboratories Limited, Bollaram Road, Miyapur, Hyderabad 500 049, India*
[b] *Chemistry Division, Institute of Science and Technology, JNT University, Kukatpally, Hyderabad 500072, Andhra Pradesh, India*
[c] *Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal, 741252, India*
[d] *Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India. E-mail: manojitpal@rediffmail.com*

† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of docking study. CCDC 822229 and 822101. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc12321a

Table 1 Effect of reaction conditions on Suzuki coupling based MCR for the preparation of pyrrole derivatives[a]



Entry	Pd catalyst (step 1)	Solvent (step 1)	%Yield[b] 5	6a
1	$PdCl_2$	DMF	0	0[c]
2	$PdCl_2$	DMF	67	15
3	$PdCl_2$	1,4-Dioxane	50	10
4	$PdCl_2$	DMF	20	70[d]
5	$PdCl_2$	No solvent	0	75[d]
6	$(PPh_3)_2PdCl_2$	No solvent	0	85
7	No Pd cat.	No solvent	10	0

[a] All the reactions were carried out using compound **1** (1.5 mmol), **2** (1.0 mmol), **3a** (1.0 mmol) and **4** (3.0 mL) in the presence of a Pd-catalyst (0.05 mol%) at 80–85 °C followed by addition of 4-methoxyphenyl boronic acid (1.2 mmol). [b] Isolated yield. [c] The reaction was carried out at room temp. [d] 0.05 mol% of $PdCl_2(PPh_3)_2$ was added after completion of the first step.

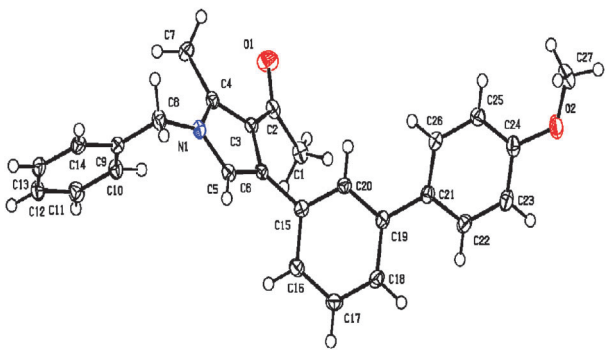


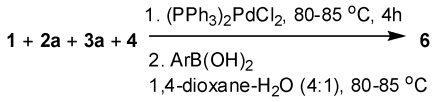
Fig. 2 X-Ray crystal structure of **6a** (ORTEP diagram). Thermal ellipsoids are drawn at a 50% probability level.

Compound **6a** was characterized by spectral and analytical data and this was supported by its molecular structure being confirmed by X-ray analysis[12] (Fig. 2).

To demonstrate the utility of present MCR a variety of 4-biaryl substituted pyrroles (**6**) were synthesized (Table 2). The use of ethylacetoacetate (**2b**) in place of **2a** and 4-bromobenzaldehyde (**3b**) in place of **3a** was examined and found to be effective (Scheme 1). The use of an aryl dioxaborolane derivative in place of aryl boronic acid was also examined (Scheme 2). Further functionalization of one of the pyrrole derivatives synthesized was carried out (Scheme 3). We then examined the feasibility of pyrrole synthesis *via* MCR based on the Heck (Scheme 4) as well as Sonogashira reaction (Tables 3 and 4).

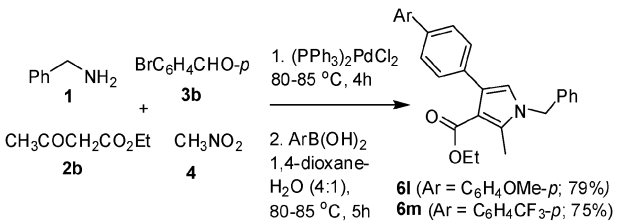
The selective inhibition of PDE4A and/or PDE4B without affecting the other isoforms (thought to be responsible for undesired side effects such as nausea and emesis) is the emerging strategy to develop a safer drug.[9a] We therefore evaluated some of the pyrroles synthesized initially for their PDE4B inhibitory potential *in vitro*. In a cell based cAMP reporter assay fold

Table 2 Synthesis of 4-biaryl substituted pyrroles (**6**)[a]

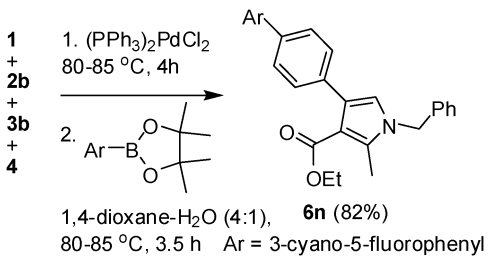


Entry	$ArB(OH)_2$; Ar=	Pyrrole (**6**)	Time[b]/h	%Yield[c]
1	C_6H_4OMe-*p*	**6a**	5.0	85
2	$C_6H_4CF_3$-*m*	**6b**	3.5	83
3	C_6H_4OMe-*o*	**6c**	5.5	81
4	C_6H_4OMe-*m*	**6d**	5.0	83
5	C_6H_4Cl-*o*	**6e**	5.5	79
6	C_6H_4Cl-*m*	**6f**	5.0	78
7	C_6H_4Cl-*p*	**6g**	5.5	80
8	$C_6H_4CF_3$-*p*	**6h**	3.5	78
9	6-Methoxypyridin-3-yl	**6i**	5.5	75
10	C_6H_3(Cl-*m*)Cl-*p*	**6j**	5.0	80
11	$C_6H_4(CH_2OH)$-*m*	**6k**	5.0	80

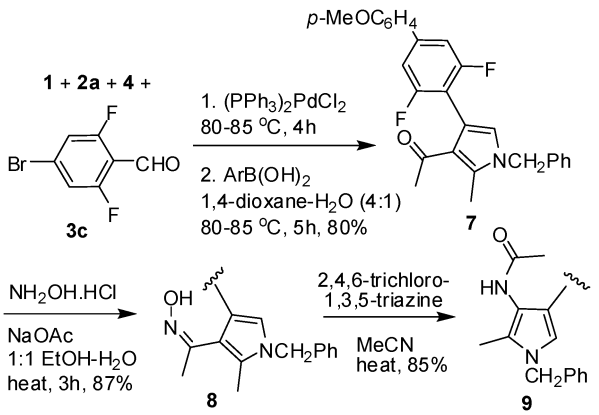
[a] All the reactions were carried out using compound **1** (1.5 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol) and **4** (3.0 mL) in the presence of a $PdCl_2(PPh_3)_2$ (0.05 mol%) at 80–85 °C followed by addition of aryl boronic acid (1.2 mmol). [b] After addition of aryl boronic acid. [c] Isolated yield.



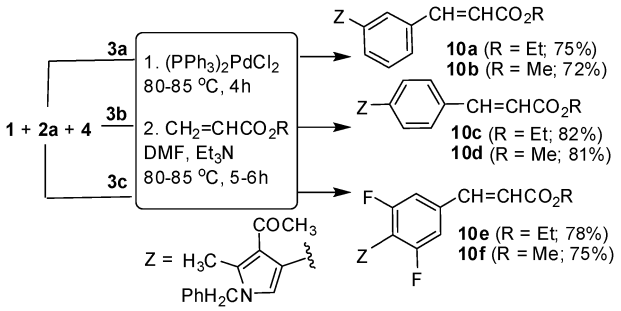
Scheme 1 Synthesis of pyrroles **6l** and **6m**.



Scheme 2 Synthesis of pyrrole **6n**.

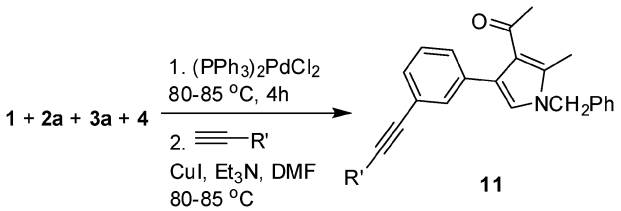


Scheme 3 Functionalization of pyrrole **7**.



Scheme 4 Synthesis of pyrrole (**10**) *via* MCR based on Heck coupling.

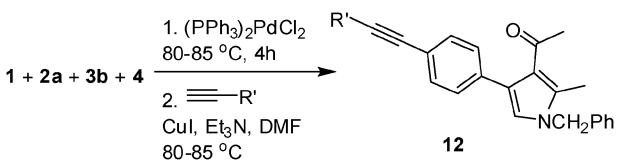
Table 3 Synthesis of 4-alkynyliaryl substituted pyrroles (**11**)[a]



Entry	HC≡CR′; R′=	Pyrrole (**11**)	Time[b]/h	%Yield[c]
1	$CH_2CH_2CH_2OH$	**11a**	5.5	81
2	CH_2CH_2OH	**11b**	5.0	86
3	$(CH_2)_5CH_3$	**11c**	4.5	81
4	$(CH_2)_3CH_3$	**11d**	4.0	94
5	CH_2OH	**11e**	6.0	80

[a] All the reactions were carried out using compound **1** (1.5 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol) and **4** (3.0 mL) in the presence of a $PdCl_2(PPh_3)_2$ (0.10 mol%) at 80–85 °C followed by addition of DMF (6 mL), a terminal alkyne (1.5 mmol), CuI (0.1 mmol), Et_3N (3.0 mmol). [b] After addition of terminal alkyne. [c] Isolated yield.

Table 4 Synthesis of 4-alkynylaryl substituted pyrroles (**12**)[a]



Entry	HC≡CR′; R′=	Pyrrole (**12**)	Time[b]/h	%Yield[c]
1	$CH_2CH_2CH_2OH$	**12a**	5.5	83
2	CH_2CH_2OH	**12b**	5.0	82
3	$(CH_2)_5CH_3$	**12c**	4.5	85
4	$C(CH_3)_2OH$	**12d**	5.5	80

[a] See the footnote of Table 3. [b] See the footnote of Table 3. [c] See the footnote of Table 3.

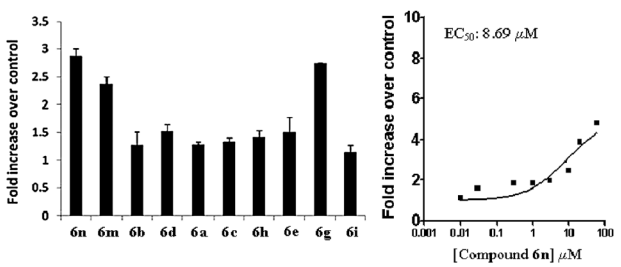


Fig. 3 PDE4B HEK 293 cell based reporter screen of **6** and EC_{50} of **6n**.

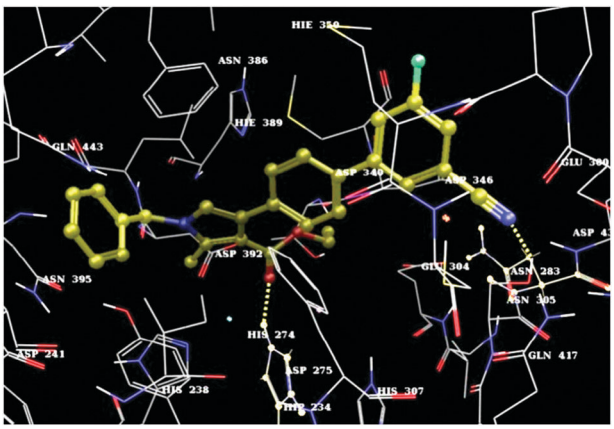


Fig. 4 Docking of **6n** at the active site of PDE4B.

elevation of the cAMP level caused by the test compounds over forskolin control was determined. Compounds **6n**, **6m** and **6g** showed significant fold increase at 30 μM whereas **6n** showed dose-dependent fold increase with an EC_{50} value of 8.69 μM (Fig. 3). This was supported by the docking results of **6n** with PDE4B protein (Fig. 4) that showed H-binding of –C═O and –CN groups of **6n** with –NH (imidazole) of Histidine234 and –OH of SER282 residues of PDE4B protein respectively (binding energy: −10.93 Kcal mol^{-1}, see ESI† for further details).

In conclusion, a general synthesis of novel 1,2,3,4-tetra substituted pyrrole derivatives has been accomplished *via* a Pd-based MCR followed by Suzuki, Heck and Sonogashira coupling in the same pot. This research has led to the identification of a pyrrole-based new inhibitor of PDE4B.

GRR thanks Dr V. Dahanukar, U. K. Syam Kumar and the analytical group of DRL MP and KVLP thanks Prof J. Iqbal.

Notes and references

1 For an excellent review, see: V. Este′vez, M. Villacampa and J. C. Mene′ndez, *Chem. Soc. Rev.*, 2010, **39**, 4402.
2 A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 1474.
3 L. Knorr, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1635.
4 C. Pall, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 367.
5 For a review, see: G. Balme, *Angew. Chem., Int. Ed.*, 2004, **43**, 6238 and references therein.
6 For recent reviews, see: (*a*) B. B. Touré and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439; (*b*) G. Balme, E. Bossharth and N. Monteiro, *Eur. J. Org. Chem.*, 2003, 4101; (*c*) C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51; (*d*) R. V. A. Orru and M. de Greef, *Synthesis*, 2003, 1471; (*e*) J. Zhu, *Eur. J. Org. Chem.*, 2003, 1133; (*f*) H. Bienaymé, C. Hulme, G. Oddon and P. Schmitt, *Chem.–Eur. J.*, 2000, **6**, 3321.
7 S. Maiti, S. Biswas and U. Jana, *J. Org. Chem.*, 2010, **75**, 1674.
8 For Pd-mediated synthesis of pyrroles, see: (*a*) R. K. Dieter and H. Yu, *Org. Lett.*, 2001, **3**, 3855; (*b*) R. Grigg and V. Savic, *Chem. Commun.*, 2000, 873; (*c*) B. Gabriele, G. Salerno and A. Fazio, *J. Org. Chem.*, 2003, **68**, 7853; (*d*) K. K. A. D. S. Kathriarachchi, A. I. Siriwardana, I. Nakamura and Y. Yamamoto, *Tetrahedron Lett.*, 2007, **48**, 2267.
9 (*a*) A. Kodimuthali, S. S. L. Jabaris and M. Pal, *J. Med. Chem.*, 2008, **51**, 5471; (*b*) S. G. Dastidar, D. Rajagopal and A. Ray, *Curr. Opin. Invest. Drugs*, 2007, **85**, 364.
10 A. M. Vignola, *Respir. Med.*, 2004, **98**, 495.
11 (*a*) G. L. Card, L. Blasdel, B. P. England, C. Zhang, Y. Suzuki, S. Gillette, D. Fong, P. N. Ibrahim, D. R. Artis, G. Bollag, M. V. Milburn, S. H. Kim, J. Schlessinger and K. Y. J. Zhang, *Nat. Biotechnol.*, 2005, **23**, 201; (*b*) F. Suzuki, T. Kuroda, T. Tamura, S. Sato, K. Ohmori and S. Ichikawa, *J. Med. Chem.*, 1992, **35**, 2863.
12 Crystallographic data (excluding structure factors) for **6a** and **6h**. CCDC 822229 and 822101, respectively (see ESI†).