Tetrahedron 65 (2009) 2751–2756

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Palladium-catalyzed intramolecular arylation of pyrimidines: a novel and expedient avenue to benzannulated pyridopyrimidines

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ARTICLE INFO

Article history:
Received 24 December 2008
Received in revised form 29 January 2009
Accepted 29 January 2009
Available online 6 February 2009

Keywords:
Heterocycles
Intramolecular arylation reaction
Palladium acetate
Pyridopyrimidine derivatives

ABSTRACT

A new efficient protocol for the synthesis of benzannulated pyrido[2,3-*d*]- and pyrido[3,2-*d*]pyrimidines has been successfully accomplished via the palladium-catalyzed intramolecular arylation of C–H bond of pyrimidine moiety. The methodology has also been extended to the synthesis of pyrimido[5,4,-*c*]isoquinoline-2,4,6(1*H*,3*H*,5*H*)-trione derivatives in excellent yields.

1. Introduction

Heterocycles containing pyrimidine as purine analogues,[1–5] especially pyrido[2,3-*d*]pyrimidines, an important biologically significant annulated pyrimidines connected with purine pteridines system,[6–8] are of great synthetic interest due to their wide biological and pharmacological activities. The potential utilities of such compounds have been identified in, virtually, all of the major therapeutic areas as many of them are found to exhibit antifolate, antibacterial, antimicrobial, anti-inflammatory, antileishmanial, anticonvulsants, diuretic and antiaggressive activities.[9–15] Moreover, pyrido[2,3-*d*]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione moiety has gained particular prominence in the field of chemotherapy as it exhibits both the properties of the biologically significant 4-hydroxy-2-pyridone and of uracil in one ring system.[16–18] Several approaches aimed towards the synthesis of these classes of compounds are available in the literature.[19–26] However, the corresponding benzannulated analogues of pyrido[2,3-*d*]- and pyrido[3,2-*d*]pyrimidines have remained unexplored for their biological activities, which may be due to the lack of general synthetic route for these classes of heteroaromatics from easily accessible precursors.

In recent years palladium-catalyzed reactions have become one of the most successful and straightforward methods for the construction of ring system as it offers an efficient entry from relatively simple precursors to cyclic compounds.[27–31] In particular, palladium catalyzed intra- and intermolecular arylation of the C–H bond of a heteroaromatic compounds is of considerable interest due to its significant utility in organic synthesis.[32–43] Although several aspects of intra- and intermolecular arylation strategies to alkenes and alkynes have been extensively investigated as it corresponds to versatile and general route to numerous oxa- and aza-heterocycles,[44–48] surprisingly, limited examples of palladium-catalyzed arylation to heterocyclic moieties are available in the literature.[49–53] However, the reactions lack in generality due to the problem of selectivity as well as harsh reaction conditions.[54–58] In the present study, we wish to report a mild, efficient and high yielding ligand free palladium-catalyzed regioselective intramolecular vinyl C–H arylation strategy for the construction of a new class of benzannulated pyridopyrimidine derivatives of biological interest.

2. Results and discussion

The requisite cyclization precursors, 5-[*N*-(2-bromobenzyl)-*N*-methylamino]-1,3-dimethyluracils (**3a**–**d**) and 6-[*N*-(2-bromobenzyl)-*N*-methylamino]-1,3-dimethyluracils (**6a**,**b**) for the present investigations were synthesized in excellent yields as depicted in Scheme 1. The compounds **3a**–**d** were obtained starting from easily available 5-bromouracil (**1**) according to our earlier published procedure[59] involving N-benzylation of 5-[*N*-methylamino]-1,3-dimethyluracil (**2**) under classical alkylation condition. In contrast, the synthesis of compound **6a**,**b** directly by the N-benzylation of 6-[*N*-methylamine]-1,3-dimethyluracil miserably failed to give any product. However, a reverse procedure, i.e., refluxing

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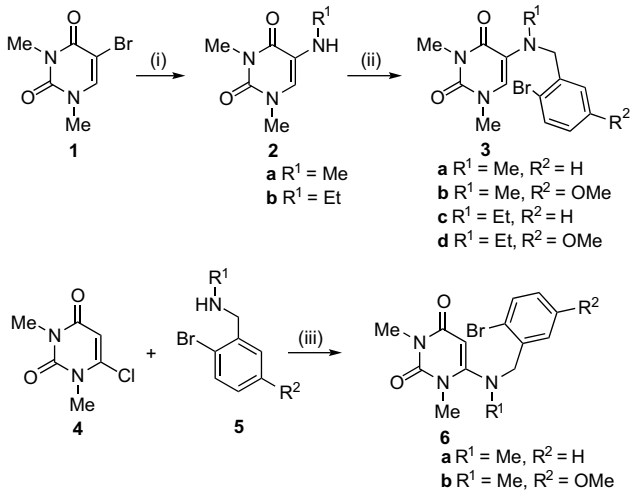
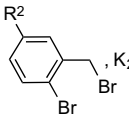
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.01.107

2-bromobenzyl-*N*-methylamine (**5**) with 6-chlorouracil (**4**) in EtOH afforded the compounds **6a**,**b** in 89% and 92% yields, respectively (Scheme 1).



Scheme 1. Reagents and conditions: (i) R^1NH_2, reflux, 1 h (ii)  , K_2CO_3 (anhyd.), acetone (dry), 8 h (iii) EtOH, reflux, 6-10 h.

During the course of our continued interest in the synthesis of substituted and condensed heteroaromatics, we have developed different novel synthetic methodologies based on free radical cyclizations[60–63] and sigmatropic rearrangements[64–67] pathways. While attempting to synthesize this particular class of benzannulated pyridopyrimidine derivatives by free radical pathway,[59,68] we observed that the reaction suffered from the mode of cyclizations (5-*exo*-*trig* vs 6-*endo*-*trig*) along with unwanted oxidation of the cyclized product[59] (Fig. 1). In view of that, we turned our attention to examining the possibility of using the palladium catalyzed intramolecular arylation reaction strategy for the synthesis of this fused pyrimidine annulated heterocycles.

In order to gain rapid insight in to the feasibility of the key cyclization, the amine **3a**, chosen as a representative substrate, was treated with $Pd(OAc)_2$ (5 mol %) as catalyst, tetra-*n*-butylammonium bromide (TBAB) as additive and potassium acetate as base in DMF at 90 °C (entry 1, Table 1) for 48 h and the desired pyridopyrimidine compound 1,3,5-trimethyl-5,6-dihydropyrimido[5,4-*c*]isoquinoline-2,4(1*H*,3*H*)-dione (**7a**) was isolated in very poor yield (15%). An optimization of the reaction condition was needed to improve the chemical yield of the transformation. The intramolecular cyclization of **3a** was also examined in CH_3CN as solvent, which also resulted in poor conversion to compound **7a**

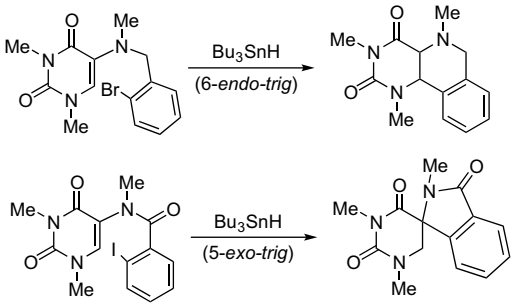
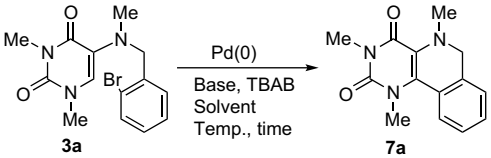


Figure 1.

Table 1
Optimization study of palladium-catalyzed intramolecular C–H arylation of 5-((2-bromobenzyl)(methyl)amino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione[a]

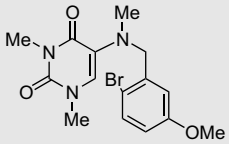
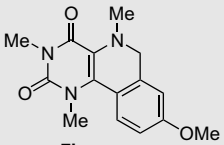
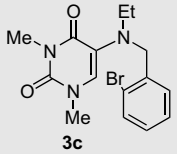
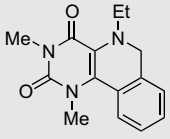
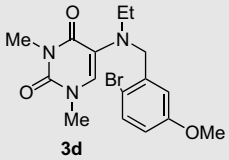
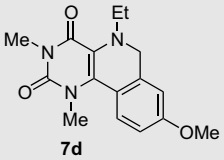
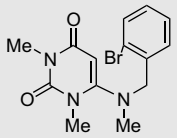
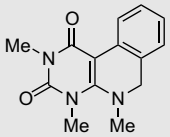
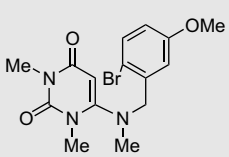
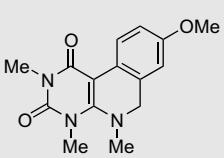


Entry	Catalyst	Mol (%)	Base	Temp (°C)	Time (h)	Solvent	Yield (%)
1	$Pd(OAc)_2$	5	KOAc	90	48	DMF	15
2	$Pd(OAc)_2$	5	KOAc	90	48	CH_3CN	10
3	$Pd(OAc)_2$	10	KOAc	90	24	DMF	30
4	$Pd(OAc)_2$	10	K_2CO_3	90	24	DMF	25
5	$Pd(OAc)_2$	10	K_2CO_3	100	12	CH_3CN	38
6	$PdCl_2$	5	K_2CO_3	100	12	DMF	0
7	$Pd(OAc)_2$	10	KOAc	100	18	Toluene	42
8	$Pd(OAc)_2$	10	KOAc	140	24	DMF	91
9	$Pd(OAc)_2$	10	KOAc	rt	72	DMF	0

[a] The amount of base and TBAB used in all cases is 2.5 mmol and 0.6 mmol, respectively.

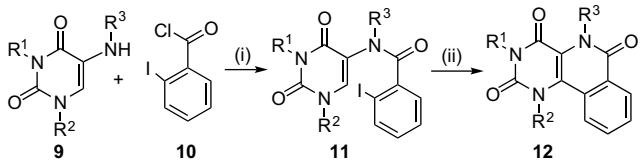
(entry 2, Table 1, yield 10%). Change of base (K_2CO_3, entry 4, Table 1) did not have any pronounced effect on the chemical yield as only 25% of the compound **7a** was isolated using 10 mol % of $Pd(OAc)_2$. The use of $PdCl_2$ also resulted no reaction (entry 6, Table 1). However, the use of 10 mol % of $Pd(OAc)_2$ in DMF with KOAc as a base

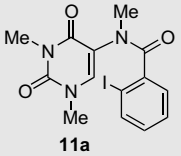
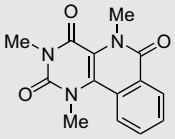
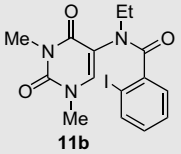
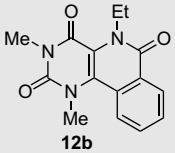
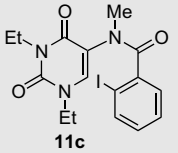
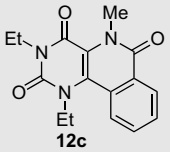
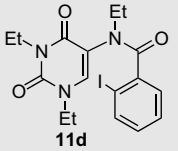
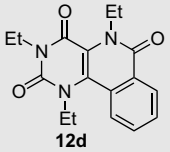
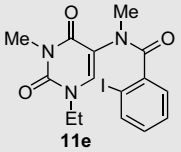
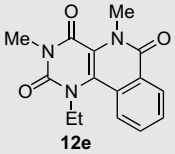
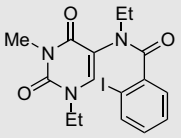
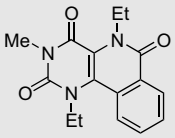
Table 2
Synthesis[a] of 5-alkyl-1,3-dimethyl-5,6-dihydropyrimido[5,4-*c*]isoquinoline-2,4(1*H*,3*H*)-diones (**7b**–**d**) and 5-alkyl-2,4-dimethyl-5,6-dihydropyrimido[4,5-*c*]isoquinoline-1,3(1*H*,3*H*)-diones

Entry	Starting material	Product	Yield[b] (%)
1	 **3b**	 **7b**	89
2	 **3c**	 **7c**	87
3	 **3d**	 **7d**	81
4	 **6a**	 **8a**	95
5	 **6b**	 **8b**	92

[a] All the reactions were carried out using $Pd(OAc)_2$ (10 mol %), KOAc (2.5 mmol), TBAB (0.60 mmol) and DMF (15 ml) at 140 °C for 24 h.
[b] Isolated yield.

Table 3
Synthesis of pyrimido[5,4-*c*]isoquinoline-2,4,6(1*H*,3*H*,5*H*)-triones (**12a–f**)



Entry	Starting material	Product	Time (h)	Yield[a] (%)
1	 **11a**	 **12a**	3	95
2	 **11b**	 **12b**	3	94
3	 **11c**	 **12c**	5	90
4	 **11d**	 **12d**	8	96
5	 **11e**	 **12e**	4	95
6	 **11f**	 **12f**	5	91

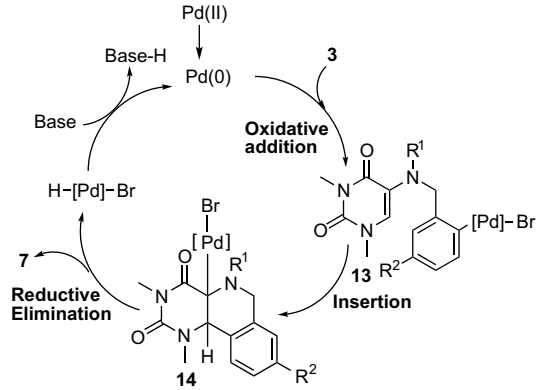
Reagents and conditions: (i) see Ref. 14; (ii) $Pd(OAc)_2$ (10 mol %), TBAB (0.60 mmol), KOAc (2.5 mmol), DMF (15 ml), 100 °C.
[a] Isolated yield.

(2.5 mmol) showed excellent conversion of **3a** to **7a** (yield: 91%) at 140 °C (entry 8, Table 1). It is noteworthy that the temperature has a pronounced effect on the cyclization as the conversion rate of **3a** was observed only 30% when 10 mol % of $Pd(OAc)_2$ was utilized at 90 °C for 24 h (entry 3, Table 1).

The intramolecular arylation reaction was applied to various substituted 5-[*N*-(2-bromobenzyl)-*N*-methylamino]-1,3-dimethyluracils (**3b–d**) and 6-[*N*-(2-bromobenzyl)-*N*-methylamino]-1,3-dimethyluracils (**6a**,**b**) utilizing optimized reaction conditions. In general, excellent yields (81–95%) of cyclized compounds, 5-alkyl-1,3-dimethyl-5,6-dihydropyrimido[5,4-*c*]isoquinoline-2,4(1*H*,3*H*)-diones (**7b–d**) and 5-alkyl-2,4-dimethyl-5,6-dihydropyrimido [4,5-*c*]isoquinoline-1,3(2*H*,4*H*)-diones (**8a**,**b**) were obtained from substrates **3b–d** and **6a**,**b**, respectively (Table 2).

We next sought to extend the scope of this methodology into the construction of pyrimido[5,4-*c*]isoquinoline-2,4,6(1*H*,3*H*,5*H*)-triones (**12a–f**), structural analogues of biologically important pyrido[2,3-*d*]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione. The precursor amides, **11a–f**, were synthesized by following the procedure developed in our laboratory.[68] The amide **11a** was initially subjected to intramolecular arylation reaction utilizing our optimized reaction condition (Table 2). Unfortunately, the cyclization using 10 mol % of $Pd(OAc)_2$ as catalyst at 140 °C for 4 h was found to be inefficient as very poor yield of the cyclized product was obtained (isolated yield of **12a**: 10%) leaving no starting material in the reaction mixture. Therefore, a further optimization study was needed. It was observed that at 100 °C with 10 mol % of $Pd(OAc)_2$ in DMF, an excellent conversion of compound **11a** to **12a** (yield 95%) was effected. By employing this new optimized reaction condition, a variety of pyrimido[5,4-*c*]isoquinoline-2,4,6(1*H*,3*H*,5*H*)-triones (**12b–f**) were prepared in 90–96% yield (Table 3).

A plausible catalytic cycle for the formation of compound **7** from the amine **3** is outlined in Scheme 2. Initial oxidative addition of palladium(0) to **3** generates the aryl-palladium intermediate **13**, which undergoes insertion into the double bond of pyrimidine to generate σ-arylpalladium complex **14**. Finally, the product is obtained via reductive elimination of H-[Pd]-Br from the palladium complex **14**. The palladium(0) species are regenerated by the base induced proton abstraction from H-[Pd]-Br.



Scheme 2. General mechanistic approach of the intramolecular arylation reaction.

3. Conclusion

In conclusion, we have developed a mild and efficient route for the construction of a new class of benzannulated pyrido[2,3-*d*]- and pyrido[3,2-*d*]pyrimidines as well as pyrimido[5,4-*c*]isoquinoline-2,4,6(1*H*,3*H*,5*H*)-triones via palladium-catalyzed intramolecular arylation of C–H bond of pyrimidine moiety under ligand free condition. The methodology, as compared to our previously reported free radical pathway, is observed to be excellent for the arylation of both at C-5 and C-6 C–H bonds of the pyrimidine heterocycles. All the reactions are clean and high yielding. The scope and generality of this methodology have been successfully demonstrated by synthesizing a variety of pyrimidine derivatives.

4. Experimental section

4.1. General

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a Perkin–Elmer L 120-000A spectrometer (ν_{max} in cm^{-1}) on KBr disks. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300 and Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as internal standard. HRMS were recorded on a QTOF Micro YA 263 instrument at the Indian Association for the Cultivation of Science, Kolkata. Silica gel [(60–120 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60 °C and 80 °C.

4.2. General procedure for the preparation of amines 3a–d

Compounds **3a–d** were prepared following our published procedure.[59]

4.2.1. 5-((2-Bromobenzyl)(ethyl)amino)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (*3c*)

Yield: 95%; sticky liquid; R_f=0.43 (30% EtOAc/pet. ether); IR (KBr) ν_{max}: 752, 1453, 1651, 1699, 2925 cm^{-1}; UV (EtOH) λ_{max}: 215, 305 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=0.98 (t, *J*=7.0 Hz, 3H, –*N*CH$_2$C***H***$_3$), 3.07 (q, *J*=7.1 Hz, 2H, –*NC****H***$_2$CH$_3$), 3.27 (s, 3H, –*NC****H***$_3$), 3.33 (s, 3H, –*NC****H***$_3$), 4.18 (s, 2H, –*NC****H***$_2$), 6.70 (s, 1H, =C***H***), 7.06–7.10 (m, 1H, Ar***H***), 7.21–7.25 (m, 1H, Ar***H***), 7.41–7.43 (dd, *J*=1.4, 7.6 Hz, 1H, Ar***H***), 7.48–7.50 (dd, *J*=1.1, 7.9 Hz, 1H, Ar***H***); HRMS Calcd for $C_{15}H_{18}N_3O_2Br$: 352.0655 [M^++H], 354.0636 [M^++H+2]. Found: 352.0625 [M^++H], 354.0625 [M^++H+2].

4.2.2. 5-((2-Bromo-5-methoxybenzyl)(ethyl)amino)-1,3-dimethylpyrimidine-4(1H,3H)-dione (*3d*)

Yield: 94%; sticky liquid; R_f=0.35 (30% EtOAc/pet. ether); IR (KBr) ν_{max}: 754, 1466, 1651, 1700, 2924 cm^{-1}; UV (EtOH) λ_{max}: 208, 306 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=0.99 (t, *J*=7.1 Hz, 3H, –*N*CH$_2$C***H***$_3$), 3.07 (q, *J*=7.1 Hz, 2H, –*NC****H***$_2$CH$_3$), 3.27 (s, 3H, –*NC****H***$_3$), 3.32 (s, 3H, –*NC****H***$_3$), 3.78 (s, 3H, –OC***H***$_3$), 4.14 (s, 2H, –*NC****H***$_2$), 6.64 (dd, *J*=3.1, 8.6 Hz, 1H, Ar***H***), 6.74 (s, 1H, =C***H***), 7.04 (d, *J*=3.0 Hz, 1H, Ar***H***), 7.36 (dd, *J*=3.4, 8.8 Hz, 1H, Ar***H***); HRMS Calcd for $C_{16}H_{20}N_3O_3Br$: 382.0761 [M^++H], 384.0742 [M^++H+2]. Found: 382.0781 [M^++H], 384.0781 [M^++H+2].

4.3. General procedure for the preparation of amines 6a,b

A mixture of 2-bromobenzyl-*N*-methylamine (**5**) (5 mmol) and 6-chlorouracil (5 mmol) was refluxed in dry EtOH (25 ml) on a water bath for 6–10 h. The reaction mixture was cooled and EtOH was removed. The residual mass was extracted with CH_2Cl_2 (3×10 ml). The CH_2Cl_2 extract was washed with water (2×10 ml) and dried (Na_2SO_4). The residual mass after removal of the solvent (CH_2Cl_2) was subjected to column chromatography over silica gel using petroleum ether/ethyl acetate as eluant to give compound (**6**), which were purified by crystallization from CH_2Cl_2.

4.3.1. 6-((2-Bromobenzyl)(methyl)amino)-1,3-dimethyl pyrimidine-2,4(1H,3H)-dione (*6a*)

Yield: 89% as yellow solid; mp 117–119 °C; R_f=0.40 (40% EtOAc/pet. ether); IR (KBr) ν_{max}: 762, 1439, 1649, 1697, 2955 cm^{-1}; UV (EtOH) λ_{max}: 214, 279 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=2.65 (s, 3H, –*NC****H***$_3$), 3.32 (s, 3H, –NC***H***$_3$), 3.37 (s, 3H, –*NC****H***$_3$), 4.16 (s, 2H, –*NC****H***$_2$), 5.30 (s, 1H, =C***H***), 7.18–7.21 (m, 1H, Ar***H***), 7.32 (d, *J*=4.2 Hz, 2H, Ar***H***), 7.57 (d, *J*=7.8 Hz, 1H, Ar***H***); HRMS Calcd for $C_{14}H_{16}N_3O_2Br$: 338.0499 [M^++H], 340.0479 [M^++H+2]. Found: 338.0530 [M^++H], 340.0517 [M^++H+2].

4.3.2. 6-((2-Bromo-5-methoxybenzyl)(methyl)amino)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (*6b*)

Yield: 92% as yellow solid; mp 109–111 °C; R_f=0.30 (40% EtOAc/pet. ether); IR (KBr) ν_{max}: 763, 1441, 1664, 1697, 2947 cm^{-1}; UV (EtOH) λ_{max}: 206, 280 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=2.66 (s, 3H, –*NC****H***$_3$), 3.32 (s, 3H, –*NC****H***$_3$), 3.36 (s, 3H, –*NC****H***$_3$), 3.78 (s, 3H, –OC***H***$_3$), 4.10 (s, 2H, –*NC****H***$_2$), 5.31 (s, 1H, =C***H***), 6.72–6.75 (dd, *J*=3, 8.7 Hz, 1H, Ar***H***), 6.88 (d, *J*=2.9 Hz, 1H, Ar***H***), 7.45 (d, *J*=8.6 Hz, 1H, Ar***H***); HRMS Calcd for $C_{15}H_{18}N_3O_3Br$: 368.0604 [M^++H], 370.0585 [M^++H+2]. Found: 368.0625 [M^++H], 370.0547 [M^++H+2].

4.4. General procedure for the preparation of compound 7a–d and 8a,b

A mixture of TBAB (tetra-*n*-butylammonium bromide) (0.19 g, 0.60 mmol) and KOAc (0.23 g, 2.5 mmol) in dry and degassed DMF (25 ml) under nitrogen atmosphere was stirred well for about 20 min. Compounds **3a–d** (0.6 mmol) and $Pd(OAc)_2$ (10 mol %) were added to it. The reaction mixture was stirred at 140 °C for 24 h and

allowed to cool to room temperature. It was diluted with water (50 ml) and extracted with CH_2Cl_2 (3×15 ml). The organic extract was washed with hydrochloric acid [1 N, 15 ml], water (20 ml) and saturated brine solution (20 ml). It was dried over anhydrous Na_2SO_4 and filtered. The residual mass after removal of the solvent was subjected to column chromatography over silica gel using petroleum ether/ethyl acetate as eluant. The crude products obtained were purified by crystallization from CH_2Cl_2/hexane mixture.

*4.4.1. 1,3,5-Trimethyl-5,6-dihydropyrimido[5,4-c]isoquinoline-2,4(1H,3H)-dione (**7a**)*

Yield: 91% as white solid; mp 147–150 °C; R_f=0.35 (40% EtOAc/pet. ether); IR (KBr) ν_{max}: 744, 1452, 1643, 1688, 2950 cm^{-1}; UV (EtOH) λ_{max}: 206, 344 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=2.51 (s, 3H, –NC***H***$_3$), 3.32 (s, 3H, –NC***H***$_3$), 3.58 (s, 3H, –NC***H***$_3$), 4.04 (s, 2H, –NC***H***$_2$), 7.26 (d, *J*=7.8 Hz, 1H, Ar***H***), 7.38–7.40 (m, 1H, Ar***H***), 7.43–7.47 (m, 1H, Ar***H***), 7.48 (d, *J*=7.8 Hz, 1H, Ar***H***); HRMS Calcd for $C_{14}H_{15}N_3O_2$: 280.1062 [M^++Na]. Found: 280.1062 [M^++Na].

*4.4.2. 8-Methoxy-1,3,5-trimethyl-5,6-dihydropyrimido[5,4-c]isoquinoline-2,4(1H,3H)-dione (**7b**)*

Yield: 89% as white solid; mp 155–158 °C; R_f=0.21 (30% EtOAc/pet. ether); IR (KBr) ν_{max}: 755, 1456, 1645, 1731, 2951 cm^{-1}; UV (EtOH) λ_{max}: 209, 344 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=2.58 (s, 3H, –NC***H***$_3$), 3.42 (s, 3H, –NC***H***$_3$), 3.56 (s, 3H, –NC***H***$_3$), 3.87 (s, 3H, –OC***H***$_3$), 4.01 (s, 2H, –NC***H***$_2$), 6.78 (d, 1H, *J*=2.4 Hz, Ar***H***), 6.88 (dd, *J*=2.5, 8.6 Hz, 1H, Ar***H***), 8.41 (d, *J*=8.7 Hz, 1H, Ar***H***); HRMS Calcd for $C_{15}H_{17}N_3O_3$: 288.1343 [M^++H]. Found: 288.1303 [M^++H].

*4.4.3. 5-Ethyl-1,3-dimethyl-5,6-dihydropyrimido[5,4-c]isoquinoline-2,4(1H,3H)-dione (**7c**)*

Yield: 87% as cream coloured solid; mp 149–151 °C; R_f=0.30 (30% EtOAc/pet. ether); IR (KBr) ν_{max}: 758, 1462, 1654, 1731, 2920 cm^{-1}; UV (EtOH) λ_{max}: 219, 353 nm; ^1H NMR ($CDCl_3$, 300 MHz): δ_H=0.85 (t, *J*=7.1 Hz, 3H, –NCH$_2$C***H***$_3$), 2.96 (q, *J*=7.0 Hz, 2H, –NC***H***$_2$CH$_3$), 3.42 (s, 3H, –NC***H***$_3$), 3.59 (s, 3H, –NC***H***$_3$), 4.12 (s, 2H, –NC***H***$_2$), 7.26 (d, *J*=1.9 Hz, 1H, Ar***H***), 7.35–7.49 (m, 3H, Ar***H***); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ_C=13.7, 28.2, 37.6, 44.4, 51.7, 123.3, 124.1, 125.9, 126.4, 127.2, 130.1, 133.5, 138.1, 152.4, 161.0; HRMS Calcd for $C_{15}H_{17}N_3O_2$: 272.1394 [M^++H]. Found: 272.1398 [M^++H].

*4.4.4. 5-Ethyl-8-methoxy-1,3-dimethyl-5,6-dihydropyrimido-[5,4-c]isoquinoline-2,4(1H,3H)-dione (**7d**)*

Yield: 81% as light brown solid; mp 132–134 °C; R_f=0.32 (40% EtOAc/pet. ether); IR (KBr) ν_{max}: 756, 1464, 1645, 1732, 2924 cm^{-1}; UV (EtOH) λ_{max}: 210, 352 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=0.85 (t, *J*=7.1 Hz, 3H, –NCH$_2$C***H***$_3$), 2.88 (q, *J*=7.1 Hz, 2H, –NC***H***$_2$CH$_3$), 3.36 (s, 3H, –NC***H***$_3$), 3.46 (s, 3H, –NC***H***$_3$), 3.83 (s, 3H, –OC***H***$_3$), 3.93 (s, 2H, –NC***H***$_2$), 6.76 (d, *J*=2.4 Hz, 1H, Ar***H***), 6.87 (dd, *J*=2.6, 8.7 Hz, 1H, Ar***H***), 7.39 (d, *J*=8.6 Hz, 1H, Ar***H***); HRMS Calcd for $C_{16}H_{19}N_3O_3$: 324.1324 [M^++Na]. Found: 324.1324 [M^++Na].

*4.4.5. 2,4,5-Trimethyl-5,6-dihydropyrimido[4,5-c]isoquinoline-1,3(2H,4H)-dione (**8a**)*

Yield: 95% as white solid; mp140–143 °C; R_f=0.46 (40% EtOAc/pet. ether); IR (KBr) ν_{max}=749, 1455, 1635, 1688, 2918 cm^{-1}; UV (EtOH) λ_{max}=205, 311 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=2.62 (s, 3H, –NC***H***$_3$), 3.43 (s, 3H, –NC***H***$_3$), 3.51 (s, 3H, –NC***H***$_3$), 4.08 (s, 2H, –NC***H***$_2$), 7.11 (d, *J*=7 Hz, 1H, Ar***H***), 7.20–7.24 (m, 1H, Ar***H***), 7.33–7.35 (m, 1H, Ar***H***), 8.43 (d, *J*=7.9 Hz, 1H, Ar***H***); HRMS Calcd for $C_{14}H_{15}N_3O_2$: 280.1062 [M^++Na]. Found: 280.1090 [M^++Na].

*4.4.6. 8-Methoxy-2,4,5-trimethyl-5,6-dihydropyrimido[4,5-c]isoquinoline-1,3(2H,4H)-dione (**8b**)*

Yield: 92% as white solid; mp 152–154 °C; R_f=0.28 (30% EtOAc/pet. ether); IR (KBr) ν_{max}=754, 1461, 1646, 1692, 2921 cm^{-1}; UV (EtOH) λ_{max}=206, 312 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=2.59 (s, 3H, –NC***H***$_3$), 3.43 (s, 3H, –NC***H***$_3$), 3.56 (s, 3H, –NC***H***$_3$), 3.81 (s, 3H, –OC***H***$_3$), 4.13 (s, 2H, –NC***H***$_2$), 6.68 (d, *J*=2.6 Hz, 1H, Ar***H***), 6.85 (dd, *J*=2.7, 8.8 Hz, 1H, Ar***H***), 8.37 (d, *J*=8.7 Hz, 1H, Ar***H***); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ_C=28.5, 32.2, 39.2, 54.9, 55.7, 99.5, 112.1, 112.9, 122.0, 126.4, 129.8, 152.1, 154.5, 158.9, 161.7; HRMS Calcd for $C_{15}H_{17}N_3O_3$: 288.1343 [M^++H]. Found: 288.1309 [M^++H].

4.5. General procedure for the preparation of compound 12a–f

A mixture of TBAB (tetra-*n*-butylammonium bromide) (0.19 g, 0.60 mmol) and KOAc (0.23 g, 2.5 mmol) in dry and degassed DMF (15 ml) was well stirred about 20 min. Compounds **11a–d** (0.6 mmol) and $Pd(OAc)_2$ (10 mol %) were added to it. The mixture was stirred at 100 °C for 3–8 h and allowed to cool to room temperature. It was diluted with water (50 ml) and extracted with $CHCl_3$ (3×10 ml). The organic extract was washed with hydrochloric acid [1 N, 15 ml], water (25 ml) and saturated brine solution (25 ml). It was dried over anhydrous Na_2SO_4 and filtered. The residual mass after removal of the solvent was subjected to column chromatography using petroleum ether/ethyl acetate as eluant over silica gel. The crude product was purified by crystallization from CH_2Cl_2/hexane mixture.

*4.5.1. 1,3,5-Trimethylpyrimido[5,4-c]isoquinoline-2,4,6(1H,3H,5H)-trione (**12a**)*

Yield: 95% as white solid; mp 171–173 °C; R_f=0.28 (40% EtOAc/pet. ether); IR (KBr) ν_{max}=741, 1461, 1656, 1708, 2959 cm^{-1}; UV (EtOH) λ_{max}=222, 350, 480 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=3.45 (s, 3H, –NC***H***$_3$), 3.75 (s, 3H, –NC***H***$_3$), 4.02 (s, 3H, –NC***H***$_3$), 7.72–7.77 (m, 2H, Ar***H***), 7.97 (d, *J*=7.8 Hz, 1H, Ar***H***), 8.56 (dd, *J*=1.4, 7.9 Hz, 1H, Ar***H***); HRMS calcd for $C_{14}H_{13}N_3O_3$: 272.1035 [M^++H]. Found: 272.1457 [M^++H].

*4.5.2. 5-Ethyl-1,3-dimethylpyrimido[5,4-c]isoquinoline-2,4,6(1H,3H,5H)-trione (**12b**)*

Yield: 94% as white solid; mp 95–97 °C; R_f=0.30 (40% EtOAc/pet. ether); IR (KBr) ν_{max}=759, 1466, 1647, 1696, 2932 cm^{-1}; UV (EtOH) λ_{max}=222, 258, 355 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=1.40 (t, *J*=6.8 Hz, 3H, –NCH$_2$C***H***$_3$), 3.45 (s, 3H, –NC***H***$_3$), 3.73 (s, 3H, –NC***H***$_3$), 4.68 (q, *J*=6.8 Hz, 2H, –NC***H***$_2$CH$_3$), 7.69–7.78 (m, 2H, Ar***H***), 7.94 (d, *J*=7.5 Hz, 1H, Ar***H***), 8.55 (dd, *J*=1.5, 7.8 Hz, 1H, Ar***H***); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ_C=15.0, 28.9, 40.7, 41.7, 118.4, 124.8, 127.8, 128.7, 129.1, 130.4, 130.6, 131.5, 152.0, 157.4, 160.5; HRMS Calcd for $C_{15}H_{15}N_3O_3$: 286.1186 [M^++H]. Found: 286.1297 [M^++H].

*4.5.3. 1,3-Diethyl-5-methylpyrimido[5,4-c]isoquinoline-2,4,6(1H,3H,5H)-trione (**12c**)*

Yield: 90% as white solid; mp 115–118 °C; R_f=0.35 (40% EtOAc/pet. ether); IR (KBr) ν_{max}=761, 1451, 1648, 1697, 2970 cm^{-1}; UV (EtOH) λ_{max}=222, 255, 352 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=1.27 (t, *J*=7.0 Hz, 3H, –NCH$_2$C***H***$_3$), 1.37 (t, *J*=6.9 Hz, 3H, –NCH$_2$C***H***$_3$), 4.01 (s, 3H, –NC***H***$_3$), 4.05 (q, *J*=7.0 Hz, 2H, –NC***H***$_2$CH$_3$), 4.22 (q, *J*=6.9 Hz, 2H, –NC***H***$_2$CH$_3$), 7.69–7.78 (m, 2H, Ar***H***), 7.91 (d, *J*=8 Hz, 1H, Ar***H***), 8.55 (dd, *J*=1.4, 7.9 Hz, 1H, Ar***H***); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ_C=12.7, 14.3, 34.2, 37.4, 47.3, 119.8, 124.4, 128.0, 128.4, 129.1, 129.7, 130.3, 131.7, 151.7, 157.4, 160.9; HRMS Calcd for $C_{16}H_{17}N_3O_3$: 322.1168 [M^++Na]. Found: 322.1152 [M^++Na].

*4.5.4. 1,3,5-Triethylpyrimido[5,4-c]isoquinoline-2,4,6(1H,3H,5H)-trione (**12d**)*

Yield: 96% as white solid; mp 192–194 °C; R_f=0.34 (40% EtOAc/pet. ether); IR (KBr) ν_{max}=761, 1459, 1651, 1697, 2942 cm^{-1}; UV (EtOH) λ_{max}=223, 260, 354 nm; ^1H NMR ($CDCl_3$, 400 MHz): δ_H=1.29 (t, *J*=7.0 Hz, 3H, –NCH$_2$C***H***$_3$), 1.36 (t, *J*=6.9 Hz, 3H, –NCH$_2$C***H***$_3$), 1.41 (t, *J*=6.8 Hz, 3H, –NCH$_2$C***H***$_3$), 4.06 (q, *J*=7.0 Hz, 2H, –NC***H***$_2$CH$_3$), 4.21

(q, J=6.9 Hz, 2H, –NC***H***$_2$CH$_3$), 4.66 (q, J=6.8 Hz, 2H, –NC***H***$_2$CH$_3$), 7.68–7.77 (m, 2H, Ar***H***), 7.89 (d, J=7.9 Hz, 1H, Ar***H***), 8.54 (dd, J=1.4, 7.9 Hz, 1H, Ar***H***); HRMS Calcd for $C_{17}H_{19}N_3O_3$: 314.1499 [M^++H]. Found: 314.1428 [M^++H].

4.5.5. 1-Ethyl-3,5-dimethylpyrimido[5,4-c]isoquinoline-2,4,6(1H,3H,5H)-trione (***12e***)

Yield: 95% as white solid; mp 165–167 °C; R_f=0.32 (40% EtOAc/pet. ether); IR (KBr) ν_{max}=759, 1456, 1647, 1697, 2976 cm^{-1}; UV (EtOH) λ_{max}=221, 253, 354 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H=1.28 (t, J=7.0 Hz, 3H, –NCH$_2$C***H***$_3$), 3.75 (s, 3H, –NC***H***$_3$), 4.03 (s, 3H, –NC***H***$_3$), 4.08 (q, J=6.9 Hz, 2H, –NC***H***$_2$CH$_3$), 7.70–7.80 (m, 2H, Ar***H***), 7.98 (d, J=7.8 Hz, 1H, Ar***H***), 8.57 (dd, J=1.4, 7.8 Hz, 1H, Ar***H***); HRMS Calcd for $C_{15}H_{15}N_3O_3$: 286.1186 [M^++H]. Found: 286.1191 [M^++H].

4.5.6. 1,5-Diethyl-3-methylpyrimido[5,4-c]isoquinoline-2,4,6(1H,3H,5H)-trione (***12f***)

Yield: 91% as white solid; mp 180–182 °C; R_f=0.35 (40% EtOAc/pet. ether); IR (KBr) ν_{max}=760, 1459, 1646, 1698, 2936 cm^{-1}; UV (EtOH) λ_{max}=222, 260, 354 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H=1.27 (t, J=7.0 Hz, 3H, –NCH$_2$C***H***$_3$), 1.41 (t, J=6.8 Hz, 3H, –NCH$_2$C***H***$_3$), 3.73 (s, 3H, –NC***H***$_3$), 4.08 (q, J=7.0 Hz, 2H, –NC***H***$_2$CH$_3$), 4.68 (q, J=6.8 Hz, 2H, –NC***H***$_2$CH$_3$), 7.69–7.78 (m, 2H, Ar***H***), 7.91 (d, J=7.8 Hz, 1H, Ar***H***), 8.55 (dd, J=1.3, 7.9 Hz, 1H, Ar***H***); HRMS Calcd for $C_{16}H_{17}N_3O_3$: 300.1343 [M^++H]. Found: 300.1346 [M^++H].

Acknowledgements

We thank the CSIR (New Delhi) and DST (New Delhi) for financial assistance. Three of us (P.K.M. and S.K.C., B.S.) are thankful to UGC (New Delhi) and CSIR (New Delhi) for their fellowships.

References and notes

1. Nasr, M. N.; Gineinah, M. M. *Arch. Pharm.* **2002**, *335*, 289.
2. Campaigne, E.; Ellis, R. L.; Bradford, M.; Ho, J. *J. Med. Chem.* **1996**, *12*, 339.
3. Figueroa-Villar, J. D.; Carueiro, C. L.; Cruz, E. R. *Heterocycles* **1992**, *34*, 891.
4. Blume, F.; Arndt, F.; Ress, R. Ger. Patent 3712782, 1998; *Chem. Abstr.* **1989**, *110*, 154312e.
5. Melik-Ogandzhonyan, R. G.; Khachatryan, V. E.; Gapoyan, A. S. *Russ. Chem. Rev.* **1985**, *54*, 262.
6. De Clercq, E.; Beraaerts, R. *J. Biol. Chem.* **1987**, *262*, 14905.
7. Brown, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 57.
8. Lunt, E. In *Comprehensive Heterocyclic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1974; Vol. 4, p 493.
9. Rosowsky, A.; Mota, C. E.; Queener, S. F. *J. Heterocycl. Chem.* **1995**, *32*, 335.
10. Donkor, I. O.; Klein, C. L.; Liang, L.; Zhu, N.; Bradley, E.; Clark, A. M. *J. Pharm. Sci.* **1995**, *84*, 661.
11. Kolla, V. E.; Deyanov, A. B.; Nazmetdinov, F. Y.; Kashina, Z. N.; Drovosekova, L. P. *Khim.-Farm. Zh.* **1993**, *27*, 29.
12. Satti, N. K.; Suri, K. A.; Sun, O. P.; Kapil, A. *Indian J. Chem., Sect. B* **1993**, *32B*, 978.
13. Nargund, L. V. G.; Reddy, Y. S. R.; Jose, R. *Indian Drugs* **1991**, *29*, 45.
14. Deyanov, A. B.; Niyazov, R. K.; Nazmetdinov, F. Y.; Syropyatov, B. Y.; Kolla, V. E.; Konshin, M. E. *Khim.-Farm. Zh.* **1991**, *25*, 26.
15. Saladowska, H.; Bartoszko-Malik, A.; Zawisza, T. *Farmaco* **1990**, *45*, 101.
16. *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck, Sharp & Dohme: Rahway, NJ, 1996; p 7657 (Piroctone); *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck, Sharp & Dohme: Rahway, NJ, 1996; p 6308 (Mocimycin), 8377 (Ricinine).
17. Knops, H. J.; Eue, L.; Schmidt, R. R.; Bayer, A. G. German Offen. DE 3210598, 1983; *Chem. Abstr.* **1984**, *100*, 4412.
18. Robins, M. J.; Kaneko, C.; Kaneko, M. *Can. J. Chem.* **1981**, *59*, 3356.
19. Wang, X. S.; Zeng, Z. S.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. *Synth. Commun.* **2005**, *35*, 1921.
20. Wang, X. S.; Zeng, Z. S.; Shi, D. Q.; Wei, X. Y.; Zong, Z. M. *Synth. Commun.* **2004**, *34*, 4331.
21. Gohain, M.; Prajapati, D.; Gogoi, B. J.; Sandhu, J. S. *Synlett* **2004**, 1179.
22. Walsh, E. B.; Wamhoff, H. *Chem. Ber.* **1989**, *122*, 1673.
23. Hirota, K.; Kuki, H.; Maki, Y. *Heterocycles* **1994**, *37*, 563.
24. Wamhoff, H.; Muhr, J. *Synthesis* **1988**, 919.
25. Subba, R. A.; Mitra, R. B. *Indian J. Chem.* **1981**, *20B*, 159.
26. Broom, A. D.; Shim, J. L.; Anderson, C. L. *J. Org. Chem.* **1976**, *411*, 1095.
27. Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.
28. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
29. Tsuji, J. *Transition Metals Reagents and Catalysts*; John Wiley & Sons: New York, NY, 2000.
30. Blame, G.; Bougssi, D.; Monteiro, N. In *Hand Book of Organopalladium Chemistry for Organic Chemistry*; Negeshi, E., Ed.; Wiley: New York, NY, 2002; Vol. II, p 2289.
31. McDaniel, K. F. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, NY, 1995; Vol. 12.
32. Majumdar, K. C.; Chattopadhyay, B.; Sinha, B. *Tetrahedron Lett.* **2008**, *49*, 1319.
33. Majumdar, K. C.; Chattopadhyay, B.; Nath, S. *Tetrahedron Lett.* **2008**, *49*, 1609.
34. Majumdar, K. C.; Chattopadhyay, B.; Ray, K. *Tetrahedron Lett.* **2007**, *48*, 7633.
35. Majumdar, K. C.; Pal, A. K.; Taher, A.; Debnath, P. *Synthesis* **2007**, 1707.
36. Arai, N.; Takahashi, M.; Mitani, M.; Mori, A. *Synlett* **2006**, 3170.
37. Karimi, B.; Enders, D. *Org. Lett.* **2006**, *8*, 1237.
38. Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5581.
39. Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395.
40. Wang, L.; Zhang, Y.; Liu, L.; Wang, Y. *J. Org. Chem.* **2006**, *71*, 1284.
41. Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 621.
42. Delest, B.; Tisserand, J.-Y.; Robert, J. M.; Nourrisson, M.-R.; Pinson, P.; Duflos, M.; Baut, G. L.; Renard, P.; Pfeiffer, B. *Tetrahedron* **2004**, *60*, 6079.
43. Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953.
44. Cropper, E. L.; White, A. J. P.; Ford, A.; Hii, K. K. *J. Org. Chem.* **2006**, *71*, 1732.
45. Leclere, J.-P.; Andre, M.; Fagnou, K. *J. Org. Chem.* **2006**, *71*, 1711.
46. Jan, N.-W.; Liu, H.-J. *Org. Lett.* **2006**, *8*, 151.
47. Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785.
48. Dyker, G. In *Hand Book Of Organopalladium Chemistry for Organic Synthesis*; Negeshi, E.-L., de Meijere, A., Eds.; Wiley: New York, NY, 2002; Vol. 1.
49. Garcia-Cuardrado, D.; Cuardro, A. M.; Atvarez-Builla, J.; Sancho, U.; Castano, O.; Vaquero, J. J. *Org. Lett.* **2006**, *8*, 5955.
50. Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827.
51. Venkatesh, C.; Sundaram, G. S. M.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2006**, *71*, 1280.
52. Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495.
53. Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem.* **2006**, *71*, 2185.
54. Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1169.
55. Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274.
56. Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.
57. Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.
58. Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.
59. Majumdar, K. C.; Mukhopadhyay, P. P. *Synthesis* **2003**, 920.
60. Majumdar, K. C.; Basu, P. K.; Chattopadhyay, S. K. *Tetrahedron* **2007**, *63*, 793.
61. Majumdar, K. C.; Alam, S. *Org. Lett.* **2006**, *8*, 4059.
62. Majumdar, K. C.; Biswas, A.; Mukhopadhyay, P. P. *Synthesis* **2003**, 2385.
63. Majumdar, K. C.; Mukhopadhyay, P. P.; Biswas, A. *Tetrahedron Lett.* **2005**, *46*, 6655.
64. Majumdar, K. C.; Chattopadhyay, S. K. *Can. J. Chem.* **2006**, *84*, 469.
65. Majumdar, K. C.; Islam, R. *Can. J. Chem.* **2006**, *84*, 1632.
66. Majumdar, K. C.; Bandyopadhyay, A.; Biswas, A. *Tetrahedron* **2003**, *59*, 5289.
67. Majumdar, K. C.; Ghosh, S. K. *Synth. Commun.* **2002**, *32*, 1271.
68. Majumdar, K. C.; Das, T. K.; Jana, M. *Synth. Commun.* **2005**, *35*, 1961.