

SYNTHESIS OF SYMMETRICAL AND NON-SYMMETRICAL 4,6-DISUBSTITUTED PYRIMIDINES BY SELECTIVE CROSS-COUPLING REACTIONS USING INDIUM ORGANOMETALLICS

M.Montserrat Martínez, José Pérez Sestelo, Luis A. Sarandeses

Departamento de Química Fundamental, Universidade da Coruña, E-15071

A Coruña, Spain

E-mail: mmartinezc@udc.es

■ ABSTRACT

The synthesis of symmetrical and non-symmetrical 4,6-disubstituted pyrimidines was performed by one-pot or stepwise palladium-catalyzed cross-coupling reactions respectively using indium reagents.

■ INTRODUCTION

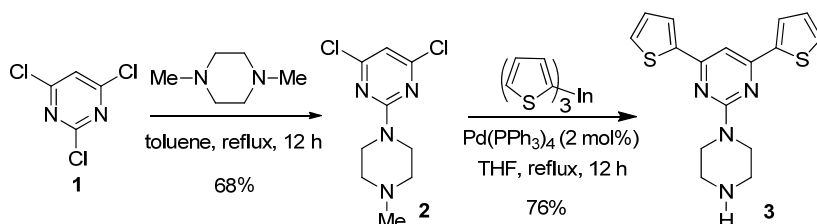
4-Substituted and 4,6-disubstituted pyrimidines bonded to an saturated heterocyclic unit at C-2 position of pyrimidine ring and related compounds has attracted much attention as potent 5-HT_{2A} receptor ligands with fairly strong behavioral antagonistic activity.¹ The role of 5-HT_{2A} receptors in the regulation of a number of processes of the central nervous system (mood, appetite, sexual behavior, learning and memory, depression, etc) and their dysfunctions (e.g. psychosis, depression, anxiety, and sleep disorders) has been well documented.² Thus, antagonists at the 5-HT_{2A} receptor sites have become of therapeutic interest for psychiatrically drugs, including atypical antipsychotic, antidepressants, and anxiolytics.³

The synthesis of these 2,4-disubstituted- and 2,4,6-trisubstituted pyrimidines has generally been carried out by three main approaches: (i) a linear synthetic sequence based on the formation of pyrimidine ring in the last steps of the synthesis⁴, (ii) condensation of α,β -unsaturated ketones with 2-(1-benzotriazolyl)acetonitrile and *sec*-amines (*N*-methylpiperazine or morpholine),⁵ or (iii) by the addition reaction of organolithium reagents across the formal N3=N4 bond in 2-chloropyrimidine followed by oxidation (aromatization).⁶ To the best of our knowledge, there has been no report in the literature regarding the synthesis of 4,6-disubstituted-2-piperazino pyrimidines or 4,6-disubstituted-2-morpholine pyrimidines by cross-coupling reaction. In this communication we present our preliminary results on the synthesis of symmetrical and non-symmetrical 4,6-disubstituted pyrimidines, bearing a piperazinyl or morpholinyl unit at C-2 position, by palladium-catalyzed cross-coupling reactions of indium organometallics with 2-substituted-4,6-dichloropyrimidines.

During the last few years, indium organometallics have been shown to be useful reagents in metal-catalyzed cross-coupling reactions.⁷ In this reaction, triorganoindium reagents can be efficiently coupled with organic halides and triflates under palladium or nickel catalysis. The main features of indium reagents in these cross-coupling reactions are their high efficiency, versatility and chemoselectivity, all the free organic groups attached to the metal atom can be efficiently transferred to the electrophile, and a wide variety of carbon groups (sp^3 , sp^2 , sp) can be transferred from the metal atom. Additionally, R_3In are particularly effective in the synthesis of functionalized heterocyclic compounds.⁸

■ RESULTS AND DISCUSSION

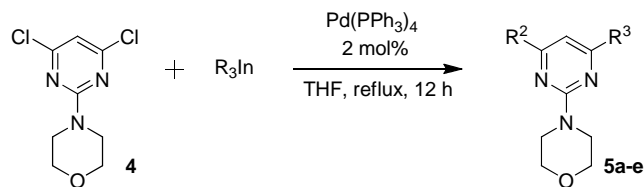
As starting point, we explored the reactivity of 4,6-dichloropyrimidine bonded to piperazine ring at C-2 position (**2**, Scheme 1) with indium organometallics in palladium-catalyzed one-pot cross-coupling reaction. Pyrimidine **2** was readily obtained in 68% yield from condensation of 2,4,6-trichloropyrimidine (**1**) with *N,N*-dimethylpiperazine in refluxing toluene for 2 h. With **2** in hand, the palladium-catalyzed cross-coupling reaction with trithienylindium (100 mol%) in presence of $Pd(PPh_3)_4$ (2 mol%) as catalyst in refluxing THF for 12 h, afforded di-coupled compound **3** in good yield (76%, demethylation occurs simultaneously of cross-coupling reaction, Scheme 1).



Scheme 1. One-pot cross-coupling reaction of pyrimidine 2 with trithienylindium.

Taking the advantage of the different groups that can be bonded to pyrimidine ring at the C-2 position, the palladium-catalyzed cross-coupling reaction of various R_3In with **4** containing a *N*-morpholine substituent at C-2 position was also studied (Table 1). On using **4** the Pd-catalyzed cross-coupling reaction with trithienyl- and tribenzo[*b*]thienylindium under the same reaction conditions described above, afforded as expected compounds **5a** and **5b** respectively in excellent yields (91-95%, Table 1, entries 1-2).

The excellent results obtained in the cross-coupling reactions of compound **4** with triheteroarylindium compounds, led to us to extend the scope of the reactivity of this electrophile to the synthesis of non-symmetrical 4,6-disubstituted pyrimidines by stepwise cross-coupling sequences. Thus, we found that the reaction of **4** with 35 mol% of tribenzo[*b*]thienylindium in the presence of $Pd(PPh_3)_4$ (2 mol%) afforded the mono-coupling product **5c** in good yield and high selectivity (74%, Table 1, entry 3).



Entry	Compound	R ¹	R ²	R ³	Product	Yield (%)
1	4			R ²	5a	91 ^a
2	4			R ²	5b	95 ^a
3	4			Cl	5c	74 ^b
4	5c				5d	86 ^c
5	5c				5e	74 ^c

^a R₃In = 100 mol%. ^b R₃In = 35 mol%, ^c R₃In = 50 mol%

Table 2. Synthesis of symmetrical and non-symmetrical 4,6-disubstituted pyrimidines by one-pot or sequential selective palladium-catalyzed cross-coupling reaction with R₃In.

Compound **5c** is a suitable substrate in a second palladium-catalyzed cross-coupling reaction and allows the synthesis of highly functionalized polyheterocycles. In this way, the reaction of **5c** with indium organometallics (50 mol%) and Pd(PPh₃)₄ (2 mol%) afforded the corresponding non-symmetrical compounds **5d** and **5e** in good yields (86-74%, Table 2, entries 4-5).

In conclusion, we have shown that symmetrical and non-symmetrical polyheteroaryls based on 4,6-disubstituted pyrimidines can be prepared in good yields from stepwise or sequential one-pot cross-coupling reaction between electron-rich and electron-poor heteroaromatics. This methodology offers a simple and high yield access to the 4,6-disubstituted pyrimidines containing a morpholine or piperazinyl ring at C-2 position which are of pharmacological interest.

■ GENERAL EXPERIMENTAL PROCEDURE

Triorganoindium reagents; General Procedure

A 25 mL round-bottomed flask containing a stir bar was charged with InCl₃ (0.35 to 1.0 mmol) and dried under vacuum with a heat gun. The mixture was cooled, a positive argon pressure was established, and anhydrous THF (4 mL) was added. The resulting solution was cooled to -78 °C and a solution of RLi (1.1 to 3.0 mmol, THF) was slowly added. The mixture was stirred for 30 minutes, the cooling bath was removed, and the reaction mixture was warmed to room temperature.

Palladium-Catalyzed Cross-Coupling Reaction: General Procedure

In a Schlenk tube, a solution of R_3In (0.35 to 1.0 mmol, ca. 0.1 M in anhydrous THF) was added to a mixture of the electrophile (1 mmol) and $Pd(PPh_3)_4$ (0.02 mmol) in anhydrous THF (4 mL). The mixture was heated under reflux until the starting material had been consumed (12 h, TLC monitoring) and the reaction was quenched by the addition of few drops of MeOH. The mixture was concentrated in vacuo and Et_2O (20 mL) was added. The organic phase was washed with sat. aq NH_4Cl (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuum. The residue was purified by flash chromatography to afford, after concentration and high-vacuum drying, the cross-coupling product.

For compound **5a**:

1H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.76 (dd, $J = 3.8, 1.1$ Hz, 2H), 7.47 (dd, $J = 5.0, 1.1$ Hz, 2H), 7.19 (s, 1H), 7.15 (dd, $J = 5.0, 3.8$ Hz, 2H), 3.94 (m, 4H), 3.83 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 161.6 (C), 159.8 (C x 2), 143.8 (C x 2), 129.0 (CH x 2), 128.0 (CH x 2), 126.5 (CH x 2), 98.8 (CH), 67.0 (CH_2 x 2), 44.2 (CH_2 x 2).

HRMS (m/z): calcd. 329.0651 for $C_{16}H_{15}ON_3S_2 [M^+]$; found: 329.0641.

■ REFERENCES

1. (a) Mokrosz, M. J.; Duszynska, B.; Klodzinska, A.; Deren-Wesolek, A.; Chojnacka-Wojcik, E.; Baranowski, T. C.; Abdou, I. M.; Redmore, N. P.; Strekowski, L. *Bioorganic & Medicinal Chemistry Letters* **1997**, *7*, 1635-1638 and references cited therein.
2. (a) Glennon, R.; Dukat, M. *ID Research Alert* **1997**, *2*, 107-113. (b) Kennett, G. A. *Current Research in Serotonin* **1998**, *3*, 1-18.
3. (a) Roth, B. L.; Willins, D. L.; Kristiansen, K.; Kroeze, W. K. *Pharmacol. Ther.* **1998**, *79*, 231-257. (b) Schechter, L. E.; McGonigle, P.; Barret, J. E. *Curr. Opin. CPNS Invest. Drugs* **1999**, *1*, 432-447. (c) Miyamoto, S.; Duncan, G. E.; Mailman, R. B.; Lieberman, J. A. *Curr. Opin. CPNS Invest. Drugs* **2000**, *2*, 25-39.
4. Agarwal, A.; Srivastava, K.; Puri, S. K.; Chauhan, P. M. S. *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 1881-1883 and references cited therein.
5. Paluchowska, M. H.; Bojarski, A. J.; Bugno, R.; Charakchieva-Minol, S.; Wesolowska, A. *Arch. Pharm. Med. Chem.* **2003**, *2*, 104-110.
6. Saczewski, J.; Paluchowska, A.; Klenc, J.; Raux, E.; Barnes, S.; Sullivan, S.; Duszynska, B.; Bojarski, A. J.; Strekowski, L. *J. Het. Chem.* **2009**, 1259-1265.
7. (a) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267-1269. (b) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155-4160. (c) Pena, M. A.; Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246-2247. (d) Pena, M. A.; Pérez Sestelo, J.; Sarandeses, L. A. *Synthesis* **2003**, 780-784. (e) Rodríguez, D.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Org. Chem.* **2004**, *69*, 8136-8139. (f) Pena, M. A.; Pérez Sestelo, J.; Sarandeses, L. A. *Synthesis* **2005**, 485-492. (g) Caeiro, J.;

Pérez Sestelo, J.; Sarandeses, L. A. *Chem. Eur. J.* **2008**, *14*, 741-746. (h) Riveiros, R.; Saya, L.; Pérez Sestelo, J.; Sarandeses, L. A. *Eur. J. Org. Chem.* **2008**, 1959-1966.

8. (a) Pena, M. A.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Org. Chem.* **2007**, *72*, 1271-1275. (b) Mosquera, A.; Riveiros, R.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **2008**, *10*, 3745-3748. (c) Bouissane, L.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **2009**, *11*, 1285-1288.

Acknowledgment: We are grateful to Ministerio de Ciencia e Innovación (Spain, CTQ2009-07130) and Xunta de Galicia (Spain, INCITE08PXIB103167PR) for financial support. MMM thanks the Xunta de Galicia for the fellowship and the Isidro Parga Pondal research contract. We also thank Prof. Mercedes Novo and Prof. Wajih Al-Soufi (Departamento de Química Física, University of Santiago de Compostela) for their helpful discussions.