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

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■ 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-HT2A receptor ligands with fairly strong behavioral antagonistic activity. 1 The role of 5-HT2A 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-HT2A 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 synthesis, 4 (ii) condensation of α,β-unsaturated ketones with 2-(1-benzotriazoyl)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. 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 tree organic groups attached to the metal atom can be efficiently transferred to the electrophile, and a wide variety of carbon groups (sp³, sp², sp) can be transferred from the metal atom. Additionally, R₃In are particulary effective in the synthesis of functionalized heterocyclic compounds.

**RESULTS AND DISCUSSION**

As starting point, we explored the reactivity of 4,6-dichloropyrimidine bonded to piperazinyl 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(PPh₃)₄ (2 mol%) as catalyst in refluxing THF for 12 h, afforded di-coupled compound 3 in good yield (76%, demetilation occurs simultaneously of cross-coupling reaction, Scheme 1).

![Scheme 1. One-pot cross-coupling reaction of pyrimidine 2 with trithienylindium.](image)

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 R₃In 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(PPh₃)₄ (2 mol%) afforded the moncoupling product 5c in good yield and high selectivity (74%, Table 1, entry 3).
**GENERAL EXPERIMENTAL PROCEDURE**

**Triorganoindium reagents; General Procedure**

A 25 mL round-bottomed flask containing a stir bar was charged with InCl$_3$ (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 R₃In (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(PPh₃)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 Et₂O (20 mL) was added. The organic phase was washed with sat. aq NH₄Cl (10 mL), dried (MgSO₄), 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:

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \] \( \delta/\text{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).} \]

\[ ^13C \text{ NMR (75 MHz, CDCl}_3 \] \( \delta/\text{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 \text{ x 2), 44.2 (CH}_2 \text{ x 2).} \]

HRMS (): calcd. 329.0651 for \( \text{C}_{16}\text{H}_{15}\text{ON}_3\text{S}_2 \) [M⁺]; found: 329.0641.

REFERENCES


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