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Site Selective Monoacylation of Pyrroles through Palladium-Catalyzed C-H Activation with Aldehydes. Synthesis of Pyrrolomycins

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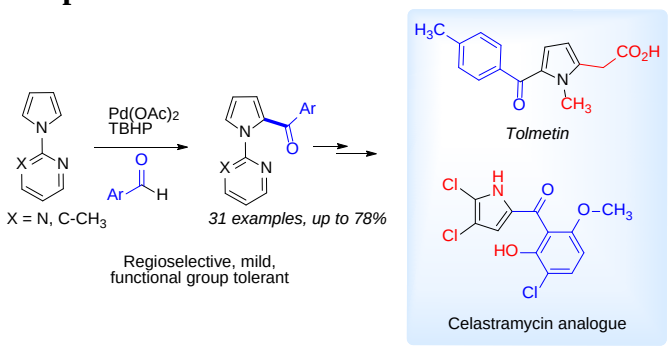
Graphical Abstract

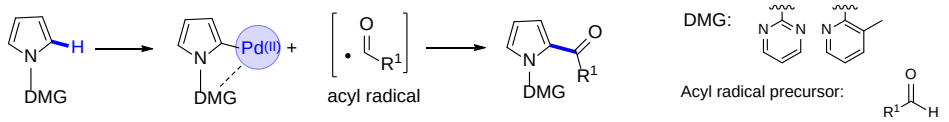


Abstract. Site selective monoacylation of pyrroles has been achieved via Pd(II)-catalyzed C-H activiation with aldehydes in the presence of TBHP as oxidant using the 3-methyl-2-pyridine as directing group. The reaction has been extended to different aromatic and heteroaromatic aldehydes for the synthesis of a series of di(hetero)aryl ketones. The utility of the methodloogy has been demonstrated in the synthesis of pyrrolomycins, as Celastramycin analogues and Tolmetin.

Introduction

The Pd(II)-catalyzed acylation of (hetero)arenes *via* C-H activation in the presence of an oxidant[1] has recently emerged as catalytic alternative to classical acylation methods (i.e. Friedel-Crafts, Vilsmeier–Haack and Houben–Hoesch reactions) for the synthesis of di(hetero)aryl ketones, whose frameworks are present in natural products, pharmaceuticals or agrochemicals. In particular, natural and synthetic molecules containing 2-aroylpyrrole cores (pyrrolomycins) have showed antibacterial, anti-fungal, and anticancer activities.[2] The procedure has been mainly applied to the C-2 selective acylation of indoles has using different directing groups and acyl sources (α-oxocarboxylic acids, aldehydes, α-diketones, and toluene derivatives). However, acylation of pyrroles is less explored, as it is neccessary to face selectivity problems, mainly due to competition with diacylation.[3] The same problem, the formation of diacylated side products, has also arosen in related systems, such as carbazoles.[4]

Therefore, we decided to investigate the Pd(II)-catalyzed C-2 monoacylation of pyrroles **1** with aldehydes, using the pyrimidin-2-yl (**1a**, X = N) and 3-methylpyridin-2-yl (**1b**, X = C–CH_3) directing groups to control site selectivity. An oxidant as TBHP will be used to generate to generate the acyl radical. Thus, under Pd(II) catalysis, the reaction would proceed via C-H activation, followed by an acyl radical capture event to give a Pd(III) or Pd(IV) intermediate that would undergo reductive elimination to provide the final product and Pd(II) (Scheme 1).[5]

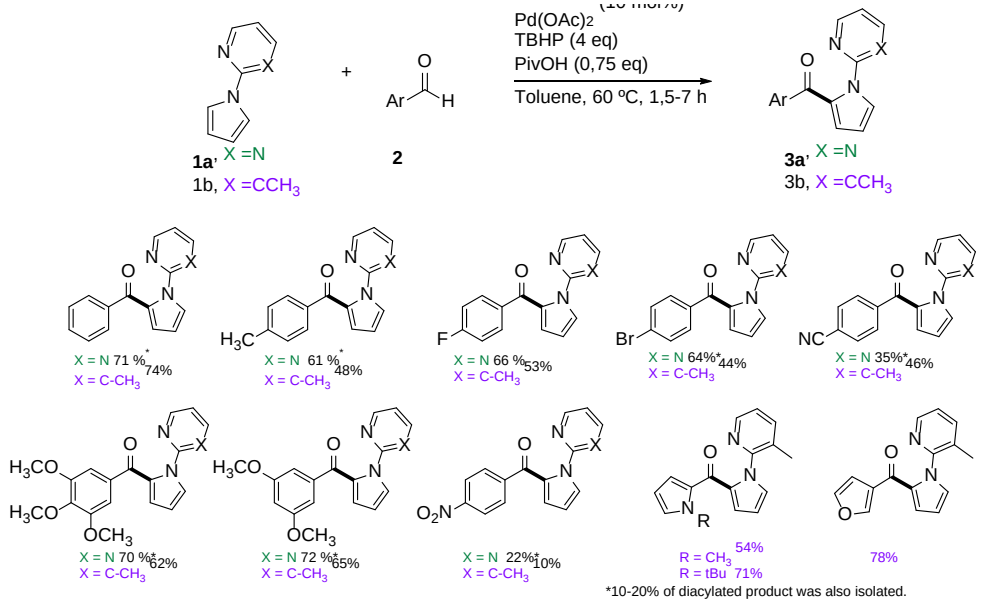


Scheme 1

Results and Discussion

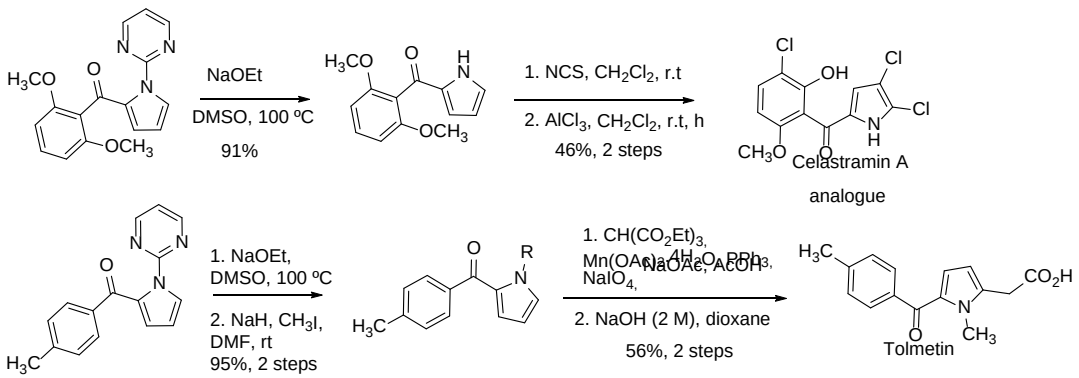
The reaction parameters (oxidant, solvent, temperature, etc.) were optimized and best results were obtained using $Pd(OAc)_2$ as catalyst, TBHP as oxidant and pivalic acid as additive, in toluene at 60ºC.

The monacylated products were obtained in moderate to good yields using both aromatic and heteroaromatic aldehydes, obtaining better yields with electron rich aromatic systems. Although with the pyrimidin-2-yl directing group diacylation could not be completely avoided, it was suppressed using the 3-methylpyridin-2yl directing group.



Scheme 2

This methology could be applied to the synthesis of an analogue of Celastramycin A, an alkaloid with high activity against a series of multiresistant bacteria and mycobacteria and potent innate immune suppressor[6] and Tolmentin, a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis, osteoarthrosis, pain,and ankylosing spondylitis (Scheme 3).[7]



Scheme 3

Conclusions

In conclusion, C-2 monoacylation of pyrroles with adehydes can be accomplished under Pd(II) catalysts [$Pd(OAc)_2$ as catalyst, TBHP as oxidant, and pivalic acid as additive). Best selectivity could be achieved using the 3-methylpyridin-2-yl as directing group. The reaction has wide scope, as it can be applied to a variety of aromatic aldehydes, bearing electron rich and electron deficient aromatic rings. The procedure can be applied to the synthesis of pyrrolomycins, as Celastramycin analogues, and an anti-inflammatory drug, Tolmetin.

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