



Directed Functionalization of Quinoxalines Aiming the Synthesis of Bioactive Compounds

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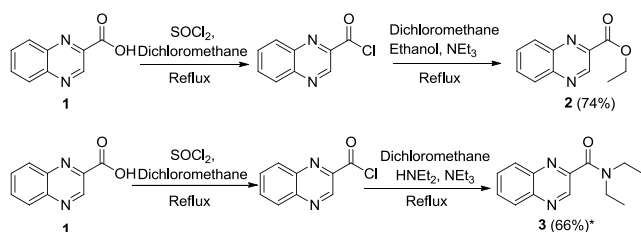
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INTRODUCTION

Access to functionalized organometallic compounds has increased considerably the scope of these nucleophilic reagents in organic synthesis. Directed metalation using mixed lithium-magnesium bases as $\text{TMPMgCl} \cdot \text{LiCl}$ are widely used for a smooth metalations of several aromatics and heterocycles with a good functional group compatibility.¹ However, deprotonation of substituted quinoxalines gave unsatisfactory results due to the high reactivity of the intermediate magnesium species.² Herein, we wish to report a direct method for the deprotonation and functionalization of some substituted quinoxalines by using $\text{TMPMgCl} \cdot \text{LiCl}$ in the presence of ZnCl_2 .

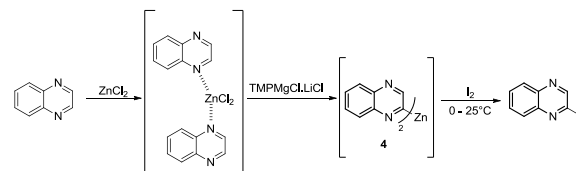
RESULTS AND DISCUSSION

An approach described by Harms has afforded 2-quinoxalinecarboxylic acid 1 in reasonable yield. From this compound we have achieved the preparation of ester and amides derivatives in good yields. Some examples are shown in Scheme 1.

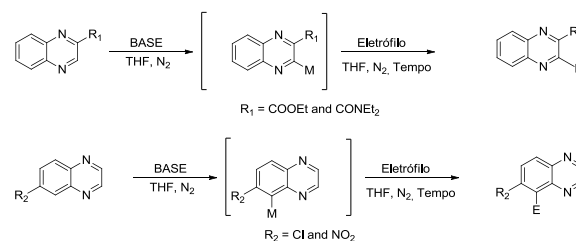


Scheme 1

A variety of functionalized quinoxalines were prepared through the reaction of the substrates with $\text{TMPMgCl} \cdot \text{LiCl}$ in the presence of ZnCl_2 followed by the reaction with electrophiles. We can consider that first the base $\text{TMPMgCl} \cdot \text{LiCl}$ reacts with heterocycle affording the organomagnesium intermediate and then a fast transmetalation with Zn occurs, leading to the quinoxalilzinc intermediate (4), which is more stable than organomagnesium intermediate (Scheme 2).



Scheme 2



Scheme 3

Some examples of functionalized quinoxalines prepared by the methodology described above are shown below:

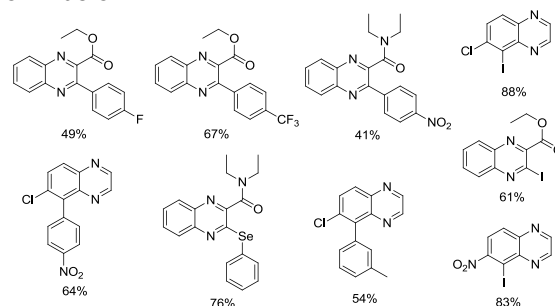


Figure 1. Products obtained by direct metalation of the substrates with $\text{TMPMgCl} \cdot \text{LiCl}$ in the presence of ZnCl_2 .

CONCLUSION

In summary, metalation of substituted quinoxalines with $\text{TMPMgCl} \cdot \text{LiCl}$ in the presence of ZnCl_2 has allowed the synthesis of highly functionalized derivatives in modest to good yields. The scope of the methodology and the application to the synthesis of bioactive compound is under investigation in our laboratories.

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