

Study and development of polar organometallic tools: synthesis of fused (hetero)aryl lactones

Sabrina TOUCHET,¹ Lynda HAMMAS,¹ Callum YEARDLEY,² Charles T. O'HARA,² Corinne COMOY¹ and Philippe C. GROS¹

¹Université de Lorraine, CNRS, L2CM, F-54000, Nancy, France

²University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK

Phthalides and derivatives are widespread in biologically active compounds and natural products. These heterocycles can also serve as versatile building blocks for the synthesis of natural and pharmaceutically-important products. Their preparation is widely documented in the literature even though many of their synthetic routes are non-convergent and relied on intramolecular cyclization, requiring relatively complex syntheses of the starting materials in order to bring diversity to the final phthalides. Moreover, fused heteroaryl-lactones (pyridinyl- and benzothienyl-) are poorly exemplified in the literature. [1,2,3,4]

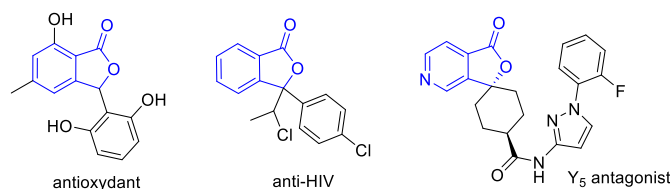


Fig. 1 Example of bioactive phthalides and pyridinic analogs.

In the past few years, our laboratory has been focusing on developing chemistry using bimetallic ate complexes composed of a polar organometallic and a “soft” organometallic in metal halogen exchange (MHE) reaction. Based on that expertise, we decided to start a research program with the aim of exploring the reactivity of organomagnesiates for the synthesis of substituted phthalides, azaphthalides and also fused benzothienyl-lactones. Thereby, we showed that BIPHEN or BINOL-based monobutylmagnesiates ((*rac*)-BIPHENBuMgLi or (*rac*)-BINOLBuMgLi) can efficiently promote the MHE of easily available 2-iodobenzoate derivatives, followed by addition of an aldehyde or a ketone which lead to an intramolecular cyclisation, and the formation of a series of new diversely substituted phthalide derivatives in moderate to good yield. [2,3,4]

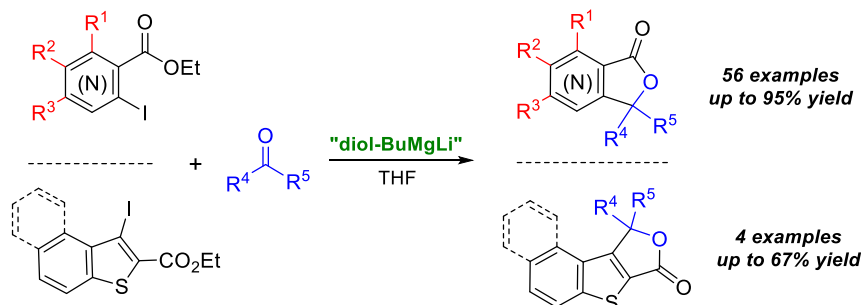


Fig. 2 Synthesis of fused (hetero)aryl lactones.

References: 1. Karmakar, R.; Pahari, P.; Mal, D., *Chem. Rev.* **2014**, *114* (12), 6213–6284. 2. Touchet, S.; Yeardeley, C.; O'Hara, C. T.; Gros, P. C., *Eur. J. Org. Chem.* **2021**, 2021, 4835–4845. 3. Hammas, L.; Touchet, S.; Adach, S.; Comoy, C., *Eur. J. Org. Chem.* **2023**, 2023, e202300800. 4. Touchet, S.; Kommidi, S. S. R.; Gros, P. C., *ChemistrySelect* **2018**, *3*, 3939–3942.

