An unusual base-sensitive beta-elimination reaction to synthesize Cinnamamides starting from common intermediate of preparing Phthalides.

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Objective
Exploration of an unusual beta-elimination reaction while resolving the low-yielding synthesis of an acetamido phthalide derivative, which was identified as a hit for developing small molecule complement component C3b modulator using a virtual screening strategy.
Methods
Several nucleophilic and non-nucleophilic bases were explored to improve the synthesis of the hit compound from either the activated ester or the acid chloride. In most cases, the reaction yielded with higher conversion to an undesired cinnamamide product. Further exploration of the undesired product opened a new avenue for the synthesis of a different class of biologically important cinnamamides. Whereas complete elimination of the bases resulted in a higher yield of the hit phthalide.
Results
Exploration of the beta-elimination led to a pathway to not only resolve the issue related to the synthesis of phthalide derivatives but also established an effective way of synthesizing cinnamamides with dissimilar substitutions. This approach creates a platform for diversified library synthesis used in SAR development.
Conclusions
Phthalides and cinnamamides are versatile building blocks used in the synthesis of several pharmaceutical drugs and are the necessary motifs in many bioactive natural products. In this present endeavor, we found an efficient one-pot synthesis of preparing both the acetamido phthalides (**2**) and the (E) cinnamamide derivatives (3) from a common intermediate 2-(3-oxo-1,3-dihydroisobenzofuranone-1yl) acetyl chloride (4) (Figure 1), just by including or eliminating the addition of-nucleophilic amines to the corresponding acid chloride.

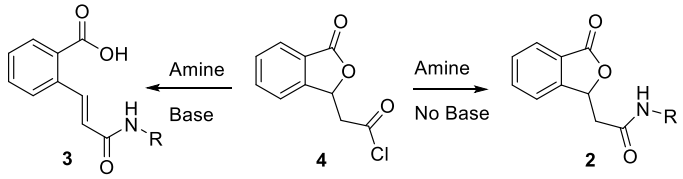

Figure 1