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Synthesis of novel 3,4,6-trisubstituted quinolines enabled by a Gould-Jacobs cyclization

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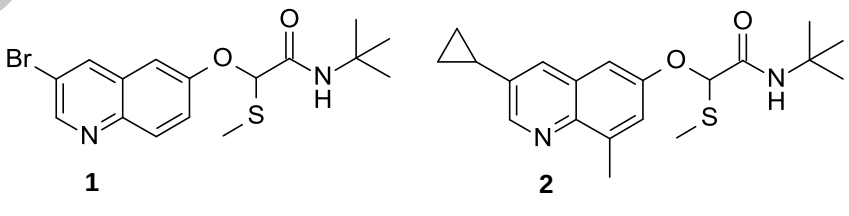
ABSTRACT

A Gould-Jacobs cyclization enabled the synthesis of several novel, so far undescribed 3,4,6-trisubstituted quinoline derivatives. They all bear substituents which are well-suited for further transformations, e.g. carboxylic acid or ester functions, halogens, terminal alkynes and hydroxyl groups. The synthesis of a highly active 3,4-disubstituted quinolin-6-yloxyacetamide fungicide gives proof of the manifold manipulations which are possible with these interesting heterobicyclic building blocks.

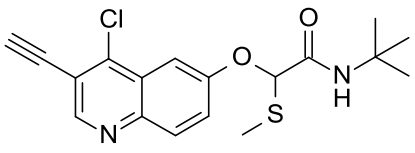
Keywords:
Quinoline
Heterocycle
Fungicide
Gould-Jacobs reaction
Cyclization

Quinoline and its derivatives not only represent one of the longest known and most published heterobicyclic systems,[1,2] many compounds bearing this scaffold have been reported to have pronounced biological activities, e.g. against cancer,[3,4] tuberculosis,[5] malaria[6] and inflammation.[7] Recently, we have reported on quinolin-6-yloxyacetamides as a new class of experimental fungicides with excellent activity against a broad range of phytopathogens from the group of Ascomycetes and Oomycetes, such as *Phytophthora infestans*, the causal agent of potato and tomato late blight, *Mycosphaerella graminicola*, the causal agent of wheat leaf blotch and *Uncinula necator*, the causal agent of grape powdery mildew.[8] Their fungicidal activity is due to their ability to inhibit the fungal tubulin polymerization, leading to microtubule destabilization. Typical examples of these quinolin-6-yloxyacetamides bear either one additional substituent in quinoline position 3, such as **1**, or two different substituents in positions 3 and 8, such as **2**.[8] The recent finding, that one of the ring carbons in **1** and **2** could be replaced by a nitrogen atom under preservation of the fungicidal activity[9] demonstrated potential scope in different, so far unexplored ring positions of the quinoline scaffold and prompted us to check novel substitution patterns. Based on our structure-activity relationship knowledge, 3,4-disubstituted quinolin-6-yloxyacetamides, such as **3**, seemed to be attractive target compounds, but were not accessible through the synthesis methodology used to obtain **1** and **2** (Figure 1).



1

2



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