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One-pot facile synthesis of polysubstituted pyridines via tandem reaction of the Blaise reaction intermediates and 3-formylchromones

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ABSTRACT

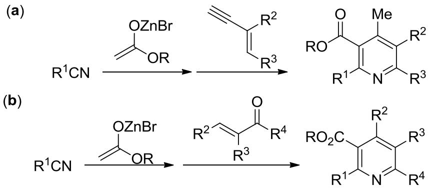
A novel tandem one-pot method for the synthesis of polysubstituted pyridine derivatives has been developed via Knoevenagel-type reaction and subsequent 6π electrocyclization of the Blaise reaction intermediates and 3-formylchromones. Short reaction time, moderate to good yields and excellent functional group tolerance have been accomplished in this protocol.

Of the *N*-heterocycles, pyridines are among the most prevalent scaffolds which are not only present in natural products, but are also widely used in functional materials, pharmaceuticals and synthetic intermediates[1]. Due to their importance, a large amount of synthetic methods have been developed for the preparation of pyridines and its derivatives. Classical methods for the synthesis of polysubstituted pyridines includes Hantzsch reaction[2], Krohnke reaction[3], Aza-Diels-Alder reaction[4]. In addition to those divergent strategies, modification of pre-existing pyridine frameworks via metal-catalyzed cross-coupling reaction to afford polysubstituted target products is also well developed[5]. Although pyridines could be generated efficiently under the above reaction conditions, difficulties arised from the preparation of starting materials, long reaction time or expensive catalysts can preclude their extensive application. Therefore, novel complementary approaches to densely substituted pyridines still remains as a hot research topic.

The classic reaction of zinc-mediated transformation of nitriles and ethyl bromoacetate, known as the Blaise reaction[6], has long been prepared corresponding β-ketoesters and β-enaminoesters[7]. In recent years, the Blaise reaction intermediates have been trapped with suitable building blocks in a tandem manner, which provided facile access to a great number of heterocyclic compounds[8]. In this regard, Lee and co-workers have developed an efficient protocol for the synthesis of polysubstituted pyridines through a tandem one-pot reaction using the Blaise reaction intermediates and 1,3-enynes[9] (Scheme 1a). In order to overcame the limitation of their previous procedure, an update of this method has been reported recently allowing diverse substitutes to be installed at the 4-position of the pyridine rings[10] (Scheme 1b).

It is well known that 3-formylchromone possessing a very reactive electrophilic center at C-2, a conjugated second carbonyl group at C-3 and an unsaturated keto function[11], have been used as an important synthetic building blocks to prepare heterocyclic compounds.

Previous work by Lee and co-works



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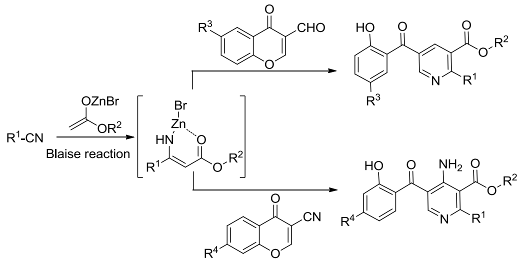

Scheme 1. Synthesis of polysubstituted pyridines via tandem reaction.

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