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A convenient synthesis of quinazoline derivatives *via* cascade imino-Diels-Alder and oxidation reaction

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Abstract

Quinazoline derivatives were synthesized from α-iminoesters *via* a cascade imino-Diels-Alder and then oxidation reaction catalyzed with $CuBr_2$. This method provided a new strategy for preparing quinazoline derivatives which may be useful in the synthesis of heterocyclic intermediates.

Keywords: Quinazolines; α-Iminoesters; Imino-Diels-Alder reaction; $CuBr_2$

Quinazoline derivatives are endowed with a large spectrum of biological activities, including remarkable anti-inflammatory activity [1], anti-cancer [2], antiviral [3] and antitubercular activity [4]. For example, gefitinib (Iressa®) and erlotinib hydrochloride (Tarceva®), which are potent inhibitors of epidermal growth factor receptor-tyrosine kinase enzymes [5] with the structure of central quinazoline units, were approved by FDA for the treatment of non-small-cell lung cancer [6]. Traditional preparations of quinazoline derivatives, including Niementowski synthesis [7], Bischler synthesis [8], Riedel synthesis [9] and modified Duff synthesis [10], suffer from limited source of starting material. From practical standpoints, it is desirable to develop new methods for the synthesis of these useful compounds.

On the other hand, imino-Diels-Alder reaction [11] that involved coupling of imines with electron rich olefins has emerged as a powerful tool for the synthesis of tetrahydroquinolines [12]. Cycloadditions of arylimines to dienophiles including enolates, thioenolates, enamines, and dienes such as cyclopentadiene and cyclohexadiene are well documented in literature (Scheme 1) [13]. Moreover, α-iminoesters have been used in synthetic organic chemistry for many years [14], such as the preparation of amino acids [15,16] and their derivatives [17]. Recently, we have synthesized a series of new compounds such as tetrasubstituted 3-alkynylpyrroles [18], β-amino esters [19], 1,4-dihydropyridines [20], chiral tricarboxylate [21] and imidazolin-4-ones [22] by using α-iminoesters as starting material. Herein, we disclose a convenient synthesis of quinazoline derivatives from α-iminoesters.

We chose aniline and ethyl glyoxalate as the substrates, and hypothesized those two molecules of α-iminoesters, which were produced *in situ* by condensation of aniline and ethyl glyoxalate, could form quinazoline derivatives **2** *via*

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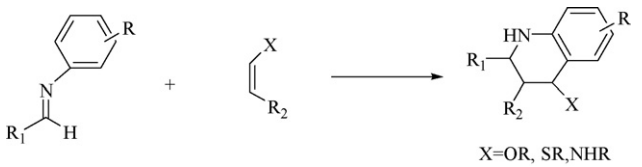
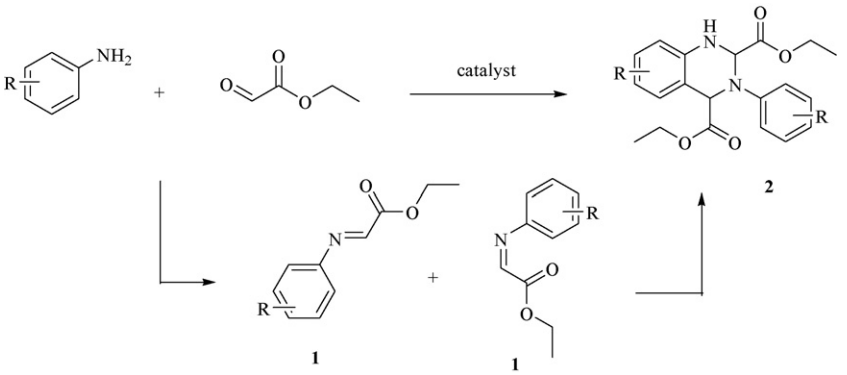


Scheme 1. Cycloadditions of arylimines to dienophiles.



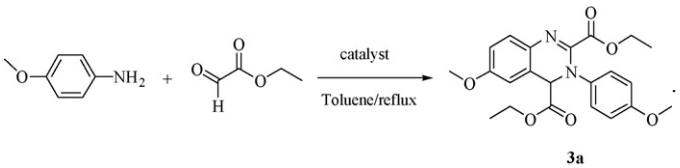
Scheme 2. Strategy of imino-Diels-Alder reaction for the synthesis of quinazoline derivatives.

imino-Diels-Alder reaction [23,13d,e], originally described by Povarov et al. (Scheme 2). However, no other product but aldimine was obtained when the reaction was carried out in toluene under refluxing for 24 h.

Efforts then were focused to find appropriate catalysts and reaction conditions to perform the proposed strategy. In the preliminary study for finding effective catalyst, we chose Lewis acids, such as $FeCl_3$, $AlCl_3$, $CuCl_2$, $Cu(OAc)_2$, $AgNO_3$, $Cu(OTf)_2$, $CuBr_2$, $ZnBr_2$, and $Sc(OTf)_3$ as candidates for this screening test (Table 1).

It was interesting that quinazoline **3a**, rather than **2**, was obtained in 76% yield when $CuBr_2$ was used as the catalyst. Other catalysts were also tested for the reaction, $AlCl_3$ and $Cu(OTf)_2$ gave product **3a** in 50% and 70% yields,

Table 1
Synthesis of quinazolines by various catalysts.[a]



3a

Entry	Catalyst	Solvent	Yield (%)[b]
1	$FeCl_3$	Toluene	ND
2	$AlCl_3$	Toluene	50
3	$CuCl_2$	Toluene	Trace
4	$AgNO_3$	Toluene	ND
5	$Cu(OAc)_2$	Toluene	ND
6	$ZnBr_2$	Toluene	Trace
7	$Sc(OTf)_3$	Toluene	Trace
8	$Cu(OTf)_2$	Toluene	70
9	$CuBr_2$	Toluene	76
10	$CuBr_2$	DMSO	72
11	$CuBr_2$	DMF	Trace

[a] Reaction conditions: amine (1.0 mmol), ethyl glyoxalate (1.2 mmol), and catalyst (0.1 mmol).
[b] Isolated yield.