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Michael Initiated Ring Closure (MIRC) reaction on in situ generated benzylidenecyclohexane-1,3-diones for the construction of chromeno[3,4-*b*]quinoline derivatives

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ABSTRACT

One-pot synthesis of chromeno[3,4-*b*]quinoline derivatives have been achieved in good yields through Michael Initiated Ring Closure (MIRC) by employing three-component condensation of aromatic aldehydes, 3-aminocoumarins, and cyclic 1,3-diketones in the presence of catalytic amount of *p*-toluenesulfonic (*p*-TSA) acid in ethanol under reflux condition. The salient features of this protocol are: simple reaction procedure, shorter reaction time, good yields, avoidance of aqueous work-up, and column-chromatographic separation. The merit of this process is highlighted by its high bond efficiency of producing three new bonds and one stereocenter in a single operation.

The Michael Initiated Ring Closure (MIRC) reaction represents an elegant approach, which has been used extensively for the construction of cyclopropane rings,[1] carbocyclic compounds,[2] and small/medium sized nitrogen[3] or oxygen[4] containing heterocyclic compounds. The MIRC reaction strategy can also be cleverly achieved through one-pot multicomponent reaction, which is gaining interest to the synthetic organic chemists in recent times.[5] Multi-component reactions (MCRs) play an important role in the modern synthetic organic chemistry as they generally occur in a single pot and exhibit high atom-economy and selectivity.[6] They also provide a powerful synthetic tool for the synthesis of diverse and complex molecules as well as small and drug-like heterocycles.[7] We have perceived that cyclic 1,3-diketones may react with various aromatic aldehydes in the presence of a suitable acid catalyst to generate benzylidenecyclohexane-1,3-dione derivatives, which might be reacted instantly with carbon nucleophile such as 3-aminocoumarin through Michael type reaction followed by ring closure reaction leading to chromeno[3,4-*b*]quinoline derivatives. The similar synthetic strategy has also been demonstrated by others for the construction of 4-aza-2,3-didehydropodophyllotoxin[8a] and tricyclic dihydropyridine analogues,[8b] and pharmacological properties of these compounds have also been studied. Compounds containing 3-aminocoumarin framework are found in many natural products and some of them are used as antibiotic and antiviral agent.[9,10] For example, novobiocine is a 3-aminocoumarin derived antibiotic which acts as an ATP-competitive inhibitor of the gyrase B subunit, blocking the negative super-coiling of relaxed DNA.[9d,10] On the other hand, the pyrido[2,3-*c*]coumarin skeleton constitutes the backbone of santiagonamine (**B**), an alkaloid (Fig. 1).[11] As a result, there is a continuing effort to prepare this class of compounds for biological studies.*p*-Toluenesulfonic acid (*p*-TSA) is a readily available chemical which has been used extensively in place of mineral acids. In recent times, it was also used as an efficient acid catalyst for the synthesis of 4(3*H*)-quinazolinones,[12] the regiospecific nitration of phenols[13] and the carbonylation of formaldehyde.[14] As a part of our ongoing efforts to develop multi-component reactions to access potentially bioactive scaffolds,[15] we would like to report one-pot three-component reaction for the synthesis of chromeno[3,4-*b*]quinoline derivatives through MIRC reaction using condensation of aromatic aldehydes, cyclic 1,3-dicarbonyl compounds and 3-aminocoumarins under reflux condition in ethanol using *p*-TSA catalyst as shown in Scheme 1.

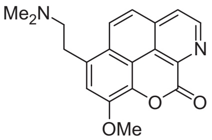

Figure 1. The naturally occurring biologically active alkaloid santiagonamine (**B**).

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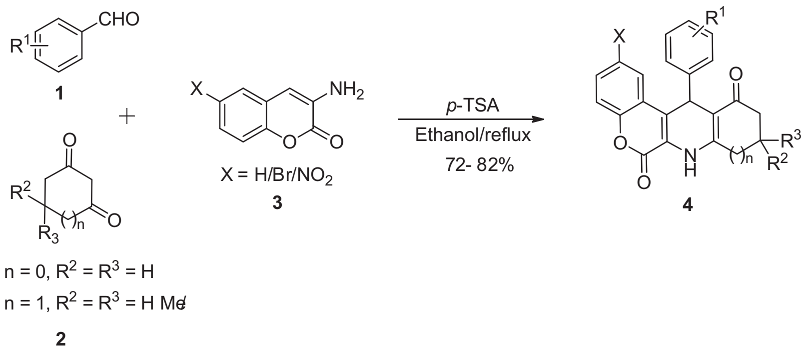


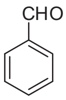
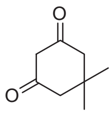
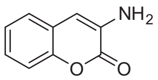
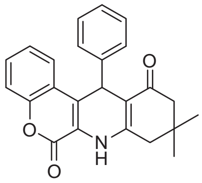
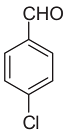
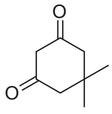
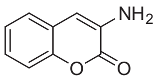
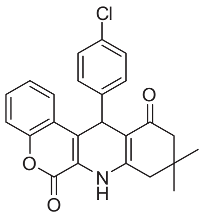
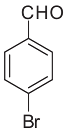
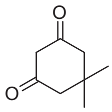
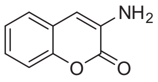
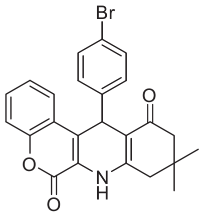
Scheme 1. One-pot three-component condensation reaction for the synthesis of chromeno[3,4-*b*]quinoline derivatives.

Table 1
Optimization of reaction conditions for the synthesis of chromeno[3,4-*b*]quinoline derivative **4a**[a]

Entry	Catalyst	Solvent	Catalyst (mol %)	Reaction condition	Time (h)	Yield[b] (%)
1	*p*-TSA	EtOH	5	Reflux	12	54
2	*p*-TSA	EtOH	10	Reflux	12	68
3	*p*-TSA	EtOH	20	Reflux	7	77
4	*p*-TSA	EtOH	30	Reflux	7	78
5	*p*-TSA	MeOH	20	Reflux	12	62
6	*p*-TSA	CH_3CN	20	Reflux	12	66
7	*p*-TSA	H_2O	20	Reflux	10	42
8	$ZnCl_2$	EtOH	20	Reflux	12	38
9	SiO_2	EtOH	20	Reflux	12	28
10	Et_3N	EtOH	20	Reflux	12	24
11	Piperidine	EtOH	20	Reflux	12	26
12	Acetic acid	EtOH	20	Reflux	24	22
13	HCl	EtOH	20	Reflux	24	00
14	No catalyst	*n*-BuOH	0	Reflux	24	00
15	*p*-TSA	*n*-BuOH	20	Reflux	4.5	75

[a] Reaction conditions: benzaldehyde, dimedone and 3-aminocoumarin were taken in 1:1:1 ratio.
[b] Isolated yields.

Table 2
Scope of various substituted chromeno[3,4-*b*]quinoline derivatives[a]

Entry	Aldehyde	1,3-Cyclic diketones	3-Aminocoumarin	Product	Time (h)	Yield[b]
1				 **4a**	7	77
2				 **4b**	8	78
3				 **4c**	8	82