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An expedient regio and diastereoselective synthesis of novel spiropyrrolidinylindenoquinoxalines via 1,3-dipolar cycloaddition reaction

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ABSTRACT

We described an efficient and multicomponent approach for the synthesis of novel polyheterocyclic spiropyrrolidinylindenoquinoxalines via 1,3 dipolar [3+2] cycloaddition reaction of 3-methyl-4-nitro-5-alkenylisoxazoles, ninhydrin, orthophenylenediamine and benzyl amine. Excellent to good yields were obtained. Various isoxazole derivatives were used as dipolarophiles against substituted benzylamine and *o*-phenylenediamine. Diastereoselectivity was found to be variable and found to be dependent on the substitutions and their position on the aromatic ring of the reactants. This catalyst free and green approach is column free and does not even require a work up procedure.

Introduction

Multi component reactions (MCRs) have become as an important tool in modern organic synthesis due to their wide functional group tolerance. These transformations are concerted and ease the process of generating libraries of important molecules.[1] A multi component reaction strategy coupled azomethine ylide mediated 1,3 dipolar [3+2] cycloaddition reaction has emerged as suitable method for synthesizing nitrogen containing complex motifs.[2] These methods have been widely applied for the synthesis of pyrrolidine containing complex molecules which is found in the core of not only natural products but also in biologically active synthetic molecules and medicinal compound.[3] Their utility in organocatalysis is well established.[4] Spiropyrrolidine scaffold is found in many pyrrolidinylspirooxindoles, which are well documented and studied synthetically because of their therapist utility and structural challenge in synthesis they pose.[3b,5] These reports include the utility of amino acid or their imines reacting with the suitable dipolarophile. However, there are few reports where benzyl amines are shown to take part in 1,3 dipolar [3+2] cycloaddition reactions leading to spiro pyrrolidines.[6]

On the other hand, indenoquinoxaline (indeno[1,2-*b*]quinoxaline) and its derivatives are synthetic in an origin and reported to possess wide range of applications.[7] Similarly 3-methyl-4-nitro-5-alkenylisoxazoles are versatile substrate and their applications as model substrate for 1,6 Michael addition, equivalent to α,β unsaturated esters[8] and 1,3 dipolar cycloaddition reactions are recently documented.[9] Recently Liu et al. has reported that 3-methyl-4-nitro-5-alkenylisoxazoles have failed to react and form spiro pyrrolidine with benzyl amine.[9a] As part of our pursuit to develop simple, convenient, green and efficient multicomponent reactions strategies,[10] herein, we report synthesis of complex, poly heterocyclic spiropyrrolidinylindenoquinoxalines with benzyl amine 3-methyl- 4-nitro- 5-alkenylisoxazoles via a four component, catalyst-free reaction (Fig. 1).

Results and discussion

We started to examine possibilities of a catalyst free, four component reaction to achieve the desired product. As it was seen from the literature, a catalyst free azomethine ylide reaction was facilitated mostly in the presence of protic solvents like methanol or

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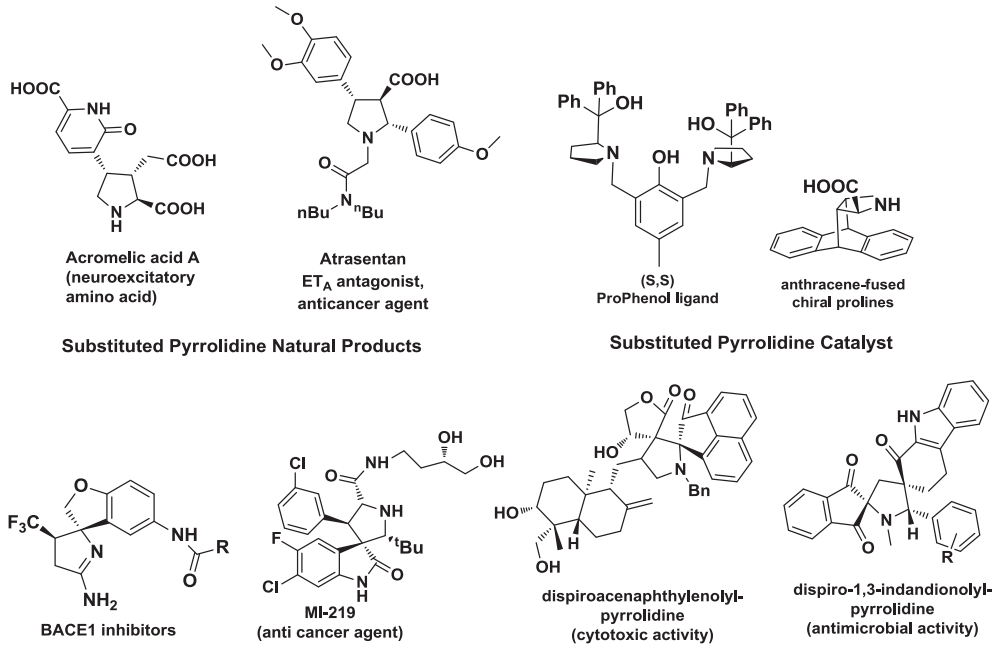


Fig. 1. Some important bioactive pyrrolidine containing molecules.

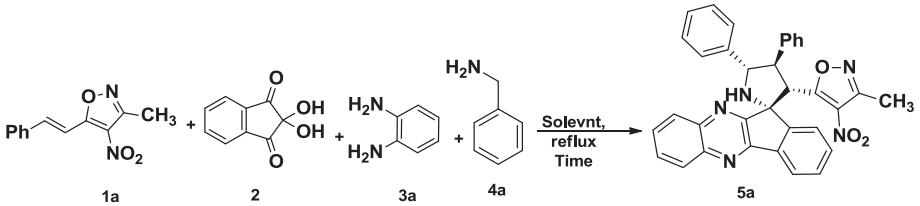
ethanol, hence they were screened primarily. Later other polar and non-polar solvents were screened for optimization of reaction conditions (Scheme 1) (Table 1). We observed initially, that the desired product was formed in 65% isolated yield as a precipitate at the bottom of reaction pot when reaction was performed in methanol (0.25 M) with equimolar concentrations of 3-methyl-4-nitro-5-alkenylisoxazole (**1a**), ninhydrin (**2**), orthophenylenediamine (**3a**) and benzyl amine (**4a**) in the indicated time (Entry 1, Table 1). Not much change in yield was observed, when the reaction was performed in ethanol even with prolonged reaction time also (Entry 2, Table 1). In an anticipation to increase the yield, the reaction was performed in polar solvents but failed to deliver the desired product in good yield (Entry 3–5, Table 1). Slight increase in the concentrations of benzyl amine and styrene has increased the yield to appreciable levels (Entry 7, Table 1). Finally, 1.5 equivalents of benzyl amine and 1.2 equivalents of styrene in 0.1 M concentration in methanol afforded the product in 85% isolated yield in 3 h (Entry 8, Table 1). There was no further improvement in the yield when the reaction was performed for prolong duration (Entry 9, Table 1).

Optimized reaction conditions accommodated an array of substrates (Scheme 2). From Table 2 it is clear that product yields and diastereoselectivity were dependent on the substitutions and their positions on all three coupling partners, i.e., 3-methyl-4-nitro-5-alkenylisoxazoles (**1a**–**k**), orthophenylenediamine (**3a**–**c**) and benzyl amine (**4a**–**c**). In case of 4-methyl diamine (**3b**) excellent yields were obtained over simple diamine (**3a**) (entry **5c** vs **5l** and **5g** vs **5n**, Table 2,). This could be reasonably attributed to the possible positive effect of electron donating groups on the diamine partner. However, 4-nitro diamine (**3c**) did not yield any product due to electron withdrawing nature of nitro group which makes the substrate labile. Halogenated styrenes (entry **5b**–**d**, Table 2) afforded better yield compared to simple styrene (entry **5a**, Table 2) and alkoxy substituted styrenes (entry **5e**–**f**, Table 2)

Table 1
Optimization of condition with various solvents.

Entry	Solvent	Time (h)	Yield %[a,b]
1	Methanol	2	65
2	Ethanol	6	68
3	DMSO	5	10
4	DMF	5	n.d[c]
5	Acetonitrile	5	33
6	Toluene	8	n.d[c]
7	Methanol	3	77[d]
8	Methanol	3	85[e]
9	Methanol	5	80[e]

[a] All reactions were carried out at 0.5 mmol scale under reflux condition for mentioned time.
[b] Isolated yield.
[c] Not determined.
[d] Performed in 0.25 M in methanol with 1 eq of ninhydrin (**2**), and orthophenylenediamine (**3a**), 1 eq of benzyl amine (**4a**) and 1.2 eq of 3-methyl-4-nitro-5-alkenylisoxazole (**1a**) added in the respective sequence.
[e] Performed at 0.1 M in methanol with 1 eq of ninhydrin and orthophenylenediamine, 1.5 eq of benzyl amine (**4a**) and 1.2 eq of 3-methyl-4-nitro-5-alkenylisoxazole (**1a**) added in the respective sequence.



Scheme 1. Optimization of reaction condition.