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Graphical Abstract

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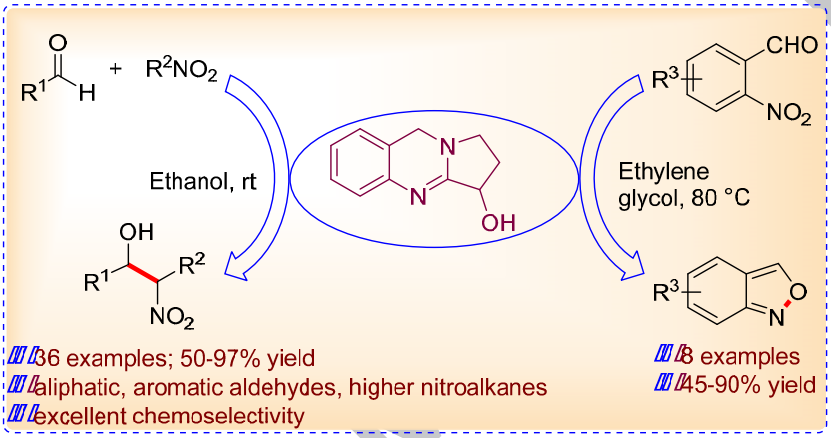

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Vasicine from *Adhatoda vasica* as an organocatalyst for metal-free Henry reaction and reductive heterocyclization of *o*-nitroacylbenzenes

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ABSTRACT

Vasicine, a quinazoline alkaloid, from the leaves of *Adhatoda vasica,* has been utilized as an efficient catalyst for metal and base free Henry reaction of various aldehydes with nitro alkanes. The method can be used in the synthesis of various *β*-nitro alcohols under mild reaction conditions without use of hazardous organic solvents and expensive catalysts. Vasicine is also applied successfully for one pot synthesis of 2,1-benzisoxazoles from *o*-nitroacylbenzenes in good yields under mild conditions.

Introduction

Over the past few decades, chemical transformations with bifunctional catalysts possessing acidic and basic sites in one scaffold has gained much attention as they have the ability of simultaneously activating both the nucleophile and electrophile in the same transition state.[1] Among them, the bifunctional catalysts based on amino alcohols or their derivatives from nature's pool (such as cinchona alkaloids, terpenes, carbohydrates, amino acids and their derivatives) have been successfully employed as organocatalyst in various organic syntheses.[2] The many advantages of these plant-derived natural products as organocatalyst include readily availability, stability, non-toxicity, sustainability, inexpensiveness and their modular structure which enable their modification for efficiency improvement. However, in nature, there is pool of scaffolds with 'privileged structure' that can be drawn as promising organocatalysts, but not explored well.

In this regard, our group is focused on exploring the potential of vasicine as organocatalyst for various organic transformations.[3,4] Vasicine is a quinazoline alkaloid abundantly available in *Adhatoda vasica* leaves and has been developed as an efficient and renewable organocatalyst for C-C bond formation[3] and reduction reaction[4] but is still in its infancy. Thus, aiming to broaden the application of vasicine in organic syntheses, the catalytic activity of vasicine is investigated for Henry reaction and reductive heterocyclization of *o*-nitroacylbenzenes.

Henry reaction is an important reaction for C-C bond formation that involves the addition of resonance stabilized anion, generated *in situ via* deprotonation of nitro alkanes to electrophilic carbonyl compounds to form *β*-nitro alcohols.[5] The resulting *β*-nitro alcohols are widely used organic intermediate that can be further transformed into a variety of synthetically important motifs such as nitro alkenes, amino alcohols, amino acids and carbonyl compounds.[6] This addition reaction is usually catalyzed by alkali metal alkoxides, transition metal complexes, or by suitable bifunctional catalyst that can simultaneously activate both the partners and bring both the reactants together[7]. Inspite of the development of various catalysts for Henry reaction, the issues of low yield, retro-aldol product formation, side product formation by Cannizaro reaction, use of hazardous solvents, additives etc. demand efforts for the development of green approaches that can selectively yield the nitroaldol product.[6a,8] Moreover, reaction with nitro alkanes other than nitromethane with *syn/anti* diastereocontrol are less studied.

Also, the reductive heterocyclization of *o*-nitroacylbenzenes is an important N-O bond formation reaction for the synthesis of 2,1-benzisoxazoles.[9] 2,1-Benzisoxazoles are an important class of heterocycles which possess important pharmacological and biological activities and are also valuable intermediate in fine organic synthesis.[10] Classical approach for the synthesis of 2,1-benzisoxazole involved the reductive cyclization of 2-acylnitrobenzene in the presence of stoichiometric amount of Sn or $SnCl_2$ in acidic medium.[11] Further advancements were made by Han *et al.,*[12] Kim *et al.*[13] and Chauhan and Fletcher[9c] in

tandem reduction-cyclization of 2-acylnitrobenzene with Sn in acidic or neutral medium and with indium/2-bromo-2-nitropropane in alcoholic or aqueous media. Other approaches towards the synthesis of 2,1-benzisoxazoles included the iron catalyzed heterocyclization of 2-azidoarylketones,[14] $BF_3{\cdot}Et_2O$ catalyzed annulation reaction of glyoxylate esters and nitrosoarenes,[15] and base mediated photochemical cyclization of 2-azidobenzoic acid[16]. Metal free reduction reactions as an alternative to metal catalyzed reactions have attracted immense attention among chemists to understand the reaction mechanisms and from green chemistry aspect. To the best of our knowledge, there is no report on metal free reductive cyclization of *o*-nitroacylbenzene to 2,1-benzisoxazole. Previously, our group investigated the vasicine catalyzed metal-free reduction of nitroarenes to corresponding aniline. Inspired by this, we anticipated if the method can be extended towards the reductive cyclization of *o*-nitroacylbenzene to corresponding benzisoxazoles.

So, in continuation of our efforts towards exploiting the potential of vasicine in coupling[3] and reduction reactions,[4] herein, we report vasicine mediated Henry reaction and reductive cyclization of *o*-nitroacylbenzene without the assistance of any transition metal catalyst under mild conditions

Results and Discussion

Henry reaction

In order to optimize the reaction conditions, initial experiments were carried out with 3-nitrobenzaldehyde and nitro methane as model substrates in the presence of vasicine and its derivatives as catalyst (Figure 1) in different solvents under varying temperature conditions (Table 1).

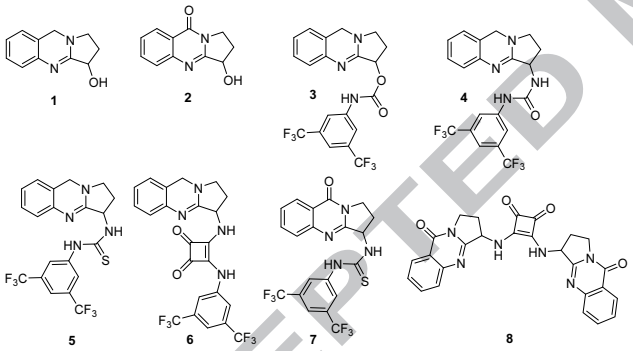
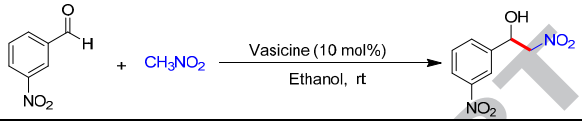


Figure 1. Structure of ligands tested.

Among all the screened ligands, only vasicine (**1**) showed higher conversion, yielding the corresponding nitro alcohol in 95% isolated yield (Table 1, entry 1). Among the different derivatives of vasicine (**3-6**), only the urea derivative of vasicine (**4**) provided the desired product in good yield (63%), whereas carbamate, thiourea and squaramides based vasicine derivatives either gave the Henry product in poor yield or no reaction was observed (Table 1, entries 3-6). The poor activity of **5** as compared to **4** may be due to the steric hindrance which hinders the Lewis basic moiety from deprotonating the nitromethane. Vasicinone and its derivatives (**2** and **7**) were found ineffective in catalyzing the reaction except for **8** (Table 1, entries 2, 7 and 8). The lower basicity of vasicinone as compared to vasicine might be responsible for its poor reactivity. After screening various catalysts, the influence of solvent was evaluated. All the tested solvents gave good yield of the product varied between 50-95%, though ethanol provided the best yield (Table 1, entries 1, 10-13). So ethanol was selected as a solvent of choice. Under neat reaction conditions, the product was obtained in 74% yield (Table 1, entry 14). After optimizing the solvent, other reaction parameters were also screened. Lowering the temperature to 0 °C afforded the product in lower yield (Table 1, entry 15). Also, lower yield was observed while decreasing the quantity of nitromethane (Table 1, entries 16 and 17).

Table 1. Optimization of reaction conditions[a]



entry	catalyst	solvent	yield (%)[b]
1	**1**	ethanol	95
2	**2**	ethanol	nr
3	**3**	ethanol	25
4	**4**	ethanol	63
5	**5**	ethanol	38
6	**6**	ethanol	32
7	**7**	ethanol	nr
8	**8**	ethanol	26
9	-	ethanol	nr
10	**1**	$CHCl_3$	66
11	**1**	toluene	68
12	**1**	THF	78
13	**1**	water	52
14	**1**	-	74
15	**1**	ethanol	58[c]
16	**1**	ethanol	72[d]
17	**1**	ethanol	48[e]
18	**1**	ethanol	90[f]
19	**1**	ethanol	65[g]

[a]Reaction conditions: 3-nitrobenzaldehyde (0.5 mmol), nitromethane (5 mmol), catalyst (0.05 mmol), ethanol (2 ml) at rt for 24 h; [b]Isolated yield; [c]Reaction carried out at 0 °C; [d]4 mmol nitromethane; [e]2.5 mmol nitromethane; [f]Reaction carried out for 12 h; [g]Reaction carried out with 5 mol% of vasicine

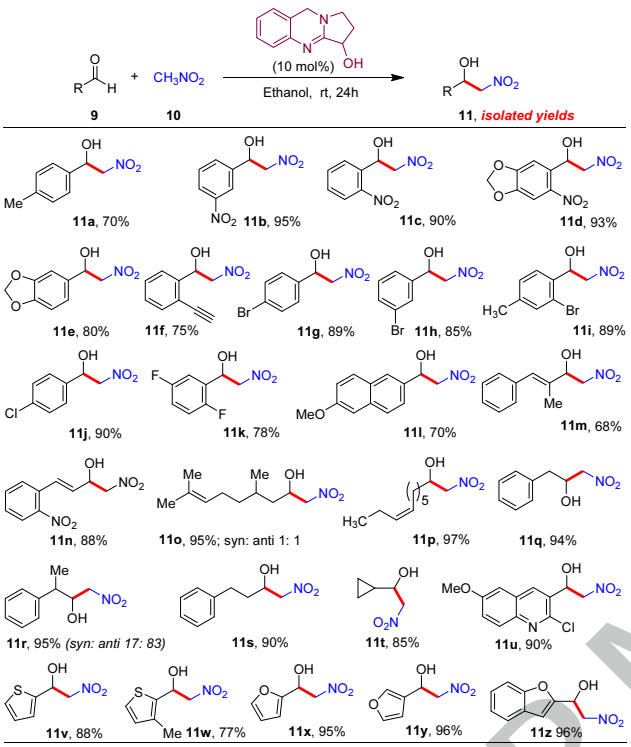
When the amount of organocatalyst was decreased from 10 mol% to 5 mol%, a lower yield was observed (Table 1, entry 19). Therefore, 10 mol% of vasicine in ethanol at room temperature was considered as optimum condition for the addition of nitroalkane to aldehydes.

With optimized conditions in hand, a variety of aliphatic as well as aromatic aldehydes were tested as substrates for the addition of nitromethane to demonstrate the reaction versatility (Table 2). It was observed that electron deficient aldehydes afforded higher yield as compared to electron rich aldehydes (Table 2, **11a**-**11n**). This may be due to increased electrophilicity of aldehydes substituted with electron-withdrawing group, thus favoring the attack of nucleophilic enolate anion to carbonyl carbon. Excellent yield was observed with current catalytic system for sterically demanding aldehydes (Table 2, **11c**, **11d**, **11f**, **11i**, **11k** and **11n**). Both unsaturated and saturated aliphatic aldehydes also gave the nitroaldol product in excellent yields (Table 2, **11o**-**11t**). Remarkably, different heterocyclic aldehydes were converted selectively to corresponding *β*-nitroalcohols in excellent yields (Table 2, **11u-11z**).

Next, the reaction was evaluated for the addition of different nitroalkanes to aldehydes. The addition of nitroethane went well to aromatic and aliphatic as well as heteroaromatic aldehydes with moderate to excellent yields (Table 3, entries **13a-13f**). Though poor diastereoselectivity was observed with aromatic aldehydes, heteroaromatic aldehydes favoured the formation of *syn* isomer (Table 3, entries **13d**-**13f**). In case of sterically

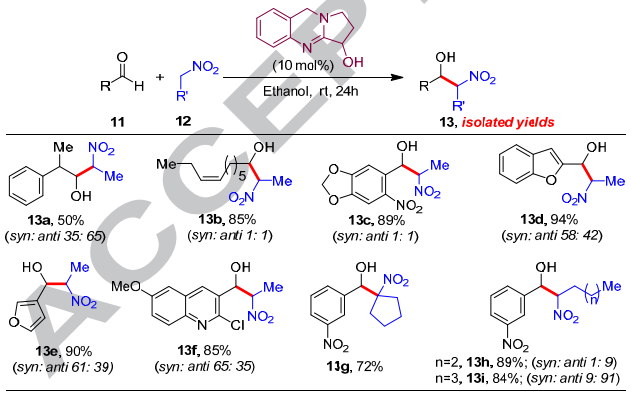
hindered nitroalkane such as 1-nitrocyclopentane, the product was observed selectively in 72% yield (Table 3, entry **13g**). The nitroaldol reaction proceeded smoothly in case of other higher nitroalkanes providing corresponding nitroalkanol in excellent yields with high anti-selectivity (Table 3, entries **13h** and **13i**).

Table 2. Scope of reaction for addition of nitromethane to different aldehydes[a]



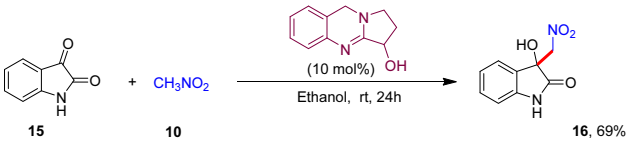
[a]Reaction conditions: aldehyde (0.5 mmol), nitromethane (5 mmol), vasicine (0.05 mmol), ethanol (2 ml) at rt for 24 h.

Table 3. Scope of reaction for addition of different nitroalkanes to aldehydes[a]



[a]Reaction conditions: aldehyde (0.5 mmol), nitromethane (5 mmol), vasicine (0.05 mmol), ethanol (2 ml) at rt for 24 h.

In all cases, the corresponding *β*-nitroalcohol was observed as sole product avoiding the formation of other possible side products. Further, the addition of nitromethane was also examined with *β*-ketoamide (isatin) as substrate and corresponding product was observed in moderate yield (Scheme 1). The product, 3-hydroxyoxyindole is core structure in various natural products.[17]



Scheme 1. Nitroaldol reaction of nitromethane with isatin.

In view of mechanism, on the basis of previous literature,[18] it is proposed that the Lewis basic nitrogen (N-4) may deprotonate the nitromethane generating the nucleophile, *i.e.* the nitromethide anion. Simultaneously, the alcoholic OH moiety may form hydrogen bond with carbonyl group of aldehyde. The nucleophilic addition of nitromethide anion to carbonyl carbon followed by reaction with protonated vasicine afforded the nitroaldol product and regeneration of vasicine. The plausible working transition model is depicted in figure 2.

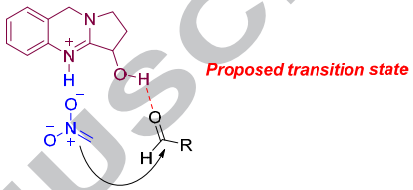
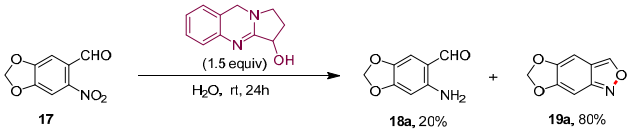


Figure 2. Plausible working transition model.

Reductive cyclization of o-nitroacylbenzenes

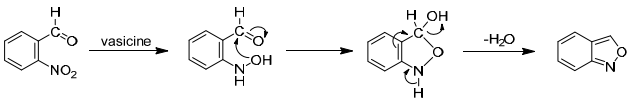
In our previous report on vasicine catalyzed reduction of nitroarenes, while attempting the reduction of 2-nitropiperonal (**17**), we observed the formation of 6*H*-1,3-dioxolo[4,5-*f*]-2,1-benzisoxazole (**19a**) as major product along with 2-aminopiperonal (**18a**) (Scheme 2).



Scheme 2. Synthesis of 6*H*-1,3-dioxolo[4,5-*f*]-2,1-benzisoxazole from 2-nitropiperonal.

The formation of 2,1-benzisoxazole in this case proceeded through the partial hydrogenation of nitro functionality with vasicine to corresponding hydroxylamine. This hydrogenation was followed by cyclization *via* attack of hydroxylamine to carbonyl moiety forming the product 2,1-benzisoxazole[11] (Scheme 3).

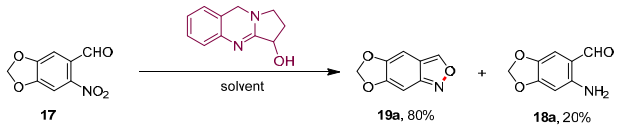
First the optimization of reaction conditions were carried out with 2-nitropiperonal (**17**) as model substrate in the presence of vasicine while varying the parameters *i.e.* solvent, temperature and catalyst loading (Table 4).



Scheme 3. Plausible mechanism for the formation of 2,1-benzisoxazole.

Reductive cyclization of **17** in presence of 1.5 equivalent of vasicine at 120 °C resulted the desired product in 80% yield along with 2-aminopiperonal in 20% yield (Table 4, entry 1).

Table 4. Optimization of reaction conditions[a]



17

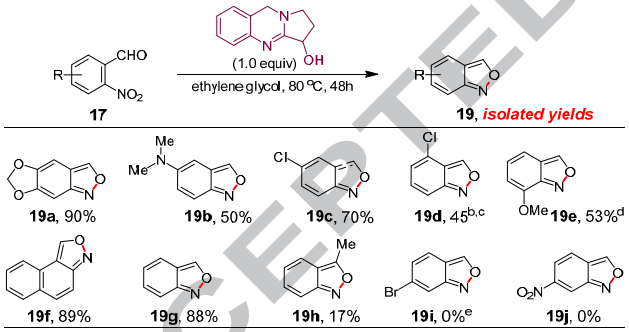
entry	catalyst	solvent	temp (°C)	yield (%)[b] 19a	18a
1	(**1**) (1.5 equiv)	water	120	80	20
2	(**1**) (1.5 equiv)	water	80	28	37
3	(**1**) (1.5 equiv)	PEG-400	80	50	50
4	(**1**) (1.5 equiv)	ethylene glycol	80	85	15
5	(**1**) (1.5 equiv)	ACN	80	73	27
6	(**1**) (1.5 equiv)	DMSO	80	39	25
7	**(1) (1.0 equiv)**	**ethylene glycol**	**80**	**95**	**0**
8	(**1**) (1.0 equiv)	ethylene glycol	50	69	11

[a]Reaction conditions: 2-nitropiperonal (0.5 mmol), vasicine (0.5 mmol), ethylene glycol (2 mL), 80 °C, 48 h; [b]Yield determined by GC anaysis.

Lowering the temperature to 80 °C resulted in lower conversion with 28% yield of **19a** (Table 4, entry 2). Further screening of different solvents revealed that reaction proceeded efficiently in ethylene glycol as solvent at 80 °C providing **19a** in good yield but **18a** was also observed as a side product (Table 4, entries 2-6). Further lowering the quantity of vasicine to 1 equivalent suppressed the formation of **18a** with **19a** as sole product (95%) (Table 4, entry 7). Lowering the temperature to 50 °C led to further decrease in the yield of **19a** (Table 4, entry 8).

With best reaction conditions in hand, the scope and limitations of the method was investigated with different 2-acylnitrobenzenes (Table 5).

Table 5. Reductive heterocylization reaction for 2,1-benzisoxazole synthesis[a]



17

[a]Reaction conditions: nitroarene (0.5 mmol), vasicine (0.5 mmol), ethylene glycol (2 mL), 80 °C, 48 h; [b]Yield determined by GC-MS; [c]2-Amino-6-chlorobenzaldehyde was isolated in 50% yield; [d]2-Amino-3-methoxybenzaldehyde was observed in 46% yield; [e]2-Amino-4-bromobenzaldehyde was isolated as major product in 65% yield.

It was observed that electron rich 2-acylnitrobenzenes resulted in the formation of 2,1-benzisoxazole in good to excellent yield (**19a-b**, **19e**). While 5-chloro-2-nitrobenzaldehyde undergoes cyclization reaction smoothly, 6-chloro-2-nitrobenzaldehyde resulted in the formation of desired product in 45% only (**19c-d**). 2-Nitronaphthaldehyde was also converted to its corresponding product in good yield (**19f**). 2-Nitrobenzaldehyde cyclized to 2,1-benzisoxazole in good yield in acetonitrile as solvent (**19g**). 2-Nitroacetophenone generated the expected product, 3-methyl-2,1-benzisoxazole, in lower yield with major product as 2-aminoacetophenone, **19h**. The reaction of 4-bromo-2-nitrobenzaldehyde led to the formation of corresponding aniline as sole product, **19i**. Unfortunately, in case of 2,4-dinitrobenzaldehyde, decomposition of substrate was observed under present reaction condition (**19j**). In case of other carbonyl groups such as acid (COOH), amide ($CONH_2$) and ester (COOR), corresponding aniline was observed as major product while, 2-nitrobenzonitrile furnished the mixture of 2-aminobenzonitrile, 2-aminobenzoic acid and 2-aminobenzamide (See supporting information).

Conclusions

In conclusion, with vasicine as organocatalyst, a simple, efficient and metal free Henry reaction of aldehydes with different nitroalkanes was demonstrated in high yields. The benefits of the protocol lie in terms of avoidance of toxic organic solvents, high yield of products and wide substrate scope with respect to aldehydes. The method was also applicable for the addition of nitromethane to *β*-ketoamide. Moreover, the competitive reactions associated with Henry reactions were also suppressed in present case. Also, various 2,1-benzisoxazoles have been synthesized from *o*-nitroacyl benzenes utilizing vasicine as hydrogen source and catalyst through a reduction-cyclization sequence in good yields. Thus, vasicine and its derivatives can be a promising tool for different coupling and reduction reactions.

Experimental section

General procedure for Henry reaction

To the solution of vasicine (0.05 mmol) in ethanol (2 mL) were added aldehyde (0.5 mmol) and nitroalkane (5 mmol) and allowed to stir at room temperature. The progress of reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under vacuo and product was purified by column chromatography over silica gel.

General procedure for reductive cyclization of o-nitrobenzaldehydes to 2,1-benzisoxazoles

The mixture of nitro compound (0.5 mmol) and vasicine (0.5 mmol) in ethylene glycol (2 mL) was stirred at 80 °C for 24-48 h. Time was not optimized separately for all substrates. After completion of reaction as monitored by TLC, the reaction mixture was allowed to cool. The reaction mixture was extracted thrice with ethyl acetate and organic layer was dried under vacuo. The product was obtained after chromatography over silica gel.

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Highlights

- Metal and base-free Henry reaction.
- Natural product as catalyst.
- Dual role of vasicine as catalyst and hydrogen source in the synthesis of 2,1-benzisoxazoles.