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Graphical Abstract

Reaction of *N*-Propargylic *β*-Enaminones with Acetylene Dicarboxylates: Catalyst-Free Synthesis of 3-Azabicyclo[4.1.0]hepta-2,4-dienes †

Kommuru Goutham,[a,b] Vemu Nagaraju,[a] Surisetti Suresh,[c] Pallepogu Raghavaiah[d] and Galla V. Karunakar,*[a,b]

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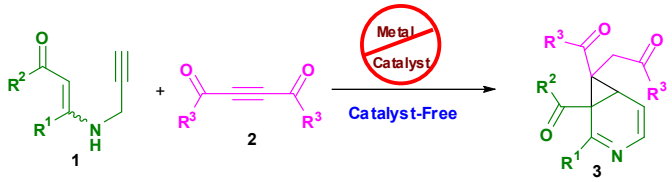

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3-Azabicyclo[4.1.0]hepta-2,4-dienes were efficiently synthesized in a reaction of *N*-propargylic *β*-enaminones and acetylene dicarboxylates by a novel and exceptionally catalyst free conditions in single step.

Heterocyclic molecules have rich chemistry.[1] Among them nitrogen heterocycles have proven as potential compounds[2] in medicinal chemistry, crop protection, and functional materials.[3] Various metal catalysed,[4] particularly transition metal catalysed[5] and organocatalysed[6] reactions were studied widely for the synthesis of nitrogen heterocycles. Finding flexible building blocks and tuning of their chemical reactivity to develop new synthetic transformations are limitless frontiers. Recent advances focus on the synthetic transformations without using metal reagents or catalysts by exploring the utilization of in-built reactivity of molecules for various interesting organic transformations.[7]

In synthetic organic chemistry, enaminones have proven as potential building blocks. The reason is enaminone exhibit dual behaviour like nucleophilic character due to enamine and electrophlic character due to enone functional groups.[8] Fine tuning the reactivity of these intermediates as building blocks for new nitrogen-containing heterocycles is of our current interest.

We were driven to explore the reactivity of *N*-propargylic *β*-enaminones **1,** which is constituted by different functional groups such as alkene, alkyne, enone, enamine, enaminone and propargylamine. Very less attention was paid on synthetic transformations of chemically diversified *N*-propargylic *β*-enaminones **1**.[9]

Gold-catalysed[10] reaction of *N*-propargylic *β*-enaminones to pyrroles was developed by Saito *et. al*.[9a] Transformation of *N*-Propargylic *β*-enaminones to pyridines and pyrroles by using CuBr and Cs_2CO_3, respectively, was developed by Cacchi *et. al*.[9b] Herein we describe metal-free, base-free reaction of *N*-propargylic *β*-enaminones **1** and dialkyl acetylene dicarboxylates **2** to furnish cycloprapane fused dihydropyridines **3** (Figure 1).

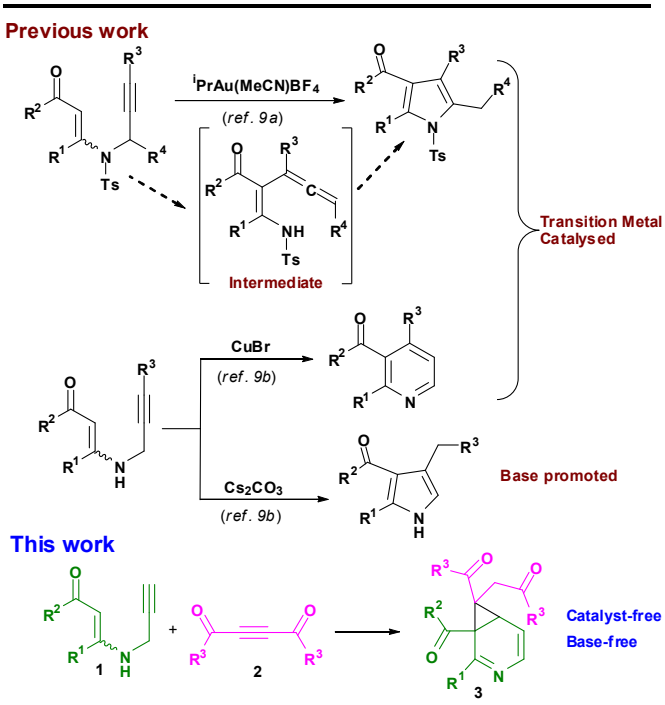

Figure 1 Transformations of *N*-propargylic *β*-enaminone **1a** to nitrogen heterocycles

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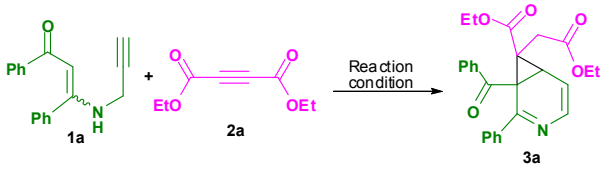
We started exploring the reactivity of *N*-propargylic *β*-enaminone **1a** towards external activated alkynes such as diethyl acetylenedicarboxylate **2a**. The results are summarised in Table 1. Our initial experiment was performed by reacting **1a** (1 equiv.) and **2a** (1 equiv.) in the presence of CuI (10 mol%) in acetonitrile solvent at 60 °C for 22 h. Very interestingly, this reaction condition gave a bicyclic product 3-azabicyclo[4.1.0]hepta-2,4-diene **3a** in 56% yield (Table 1, entry 1). The reaction of **1a** and **2a** in the presence of 10 mol% of $AgSbF_6$ gave product **3a** in 64% yield (Table 1, entry 2).

Table 1 Optimisation studies



Entry	Catalyst (mol%)	Solvent	T (°C)	Time (h)	Yield (%)[a]
1	CuI (10)	CH_3CN	60	22	56
2	$AgSbF_6$ (10)	CH_3CN	60	22	64
3	$AuCl(PPh_3)$ (10)	CH_3CN	60	42	61
4	$AuCl_3$/ $AgSbF_6$ (5/15)	CH_3CN	60	18	45
5	$Zn(OTf)_2$ (10)	CH_3CN	60	24	52
6	SiO_2 (10)	CH_3CN	60	48	73
7	Cs_2CO_3 (1 equiv)	CH_3CN	60	48	nr
8	K_2CO_3 (1 equiv)	CH_3CN	60	48	nr
9	---	CH_3CN	60	4	91
10	---	No Solvent	60	3	32
11	---	H_2O	30	4	25
12	---	EtOH	90	24	27
13	---	EtOAc	60	36	60
14	---	DMF	80	20	12
15	---	THF	60	24	45
16	---	1,4-dioxane	70	20	47
17	---	CH_2Cl_2	40	24	29
18	---	$CHCl_3$	70	20	23
19	---	Toluene	90	20	31
20	---	EtOAc/CH_3CN (1:1)	60	28	80

Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), solvent (3 mL); All reactions were conducted under nitrogen atmosphere. [a]Isolated product yield of **3a**. nr: no reaction.

Reaction of *N*-propargylic *β*-enaminones **1a** (1 equiv.) with diethyl acetylenedicarboxylate **2a** (1 equiv.) was tested in the presence of PPh_3AuCl (10 mol%) in acetonitrile at 60 °C for 42 h, the corresponding product **3a** was isolated in 61% yield (Table 1, entry 3). Experiments were conducted by utilizing catalysts such as $AuCl_3/AgSbF_6$ and $Zn(OTf)_2$ in acetonitrile solvent at 60 °C. These conditions gave product **3a** in lower yields (Table 1, entries 4 and 5). When the reaction of **1a** and **2a** was performed by utilizing 10 mol% of SiO_2 gave the product **3a** in 73% yield (Table 1, entry 6). We have also conducted experiments for the reaction of **1a** and **2a** in the presence of two different bases such as Cs_2CO_3 and K_2CO_3. Both of these reactions did not proceed to yield the desired product **3a** (Table 1, entries 7 and 8).

We became interested in testing this reaction in the absence of catalyst to know the effect of the catalyst in this synthetic transformation. Accordingly, we have further performed the reaction of **1a** and **2a** in acetonitrile without using any catalyst. To our surprise the product **3a** yield (91%) was improved significantly in 4 hours of reaction time (Table 1, entry 9).

Then we conducted the reaction of **1a** and **2a** without using any catalyst or any solvent. In this case the product **3a** was isolated in only 32% yield (Table 1, entry 10). Different solvents were taken in to consideration to improve the yields of product **3a**. In the case of water used as a solvent, only 25% of **3a** was isolated (Table 1, entry 11). When ethanol was used as a solvent 27% yield of product **3a** was isolated (Table 1, entry 12). Ethyl acetate was used as a solvent and the product **3a** was isolated in 60% yield (Table 1, entry 13). When DMF was used as a solvent, the product **3a** was isolated in only 12% yield (Table 1, entry 14). The above reaction was conducted by using THF and 1,4-dioxane as solvents, the corresponding product **3a** was isolated in 45% and 47% yields, respectively (Table 1, entries 15 and 16). Reaction of **1a** with **2a** was conducted in dichloromethane and chloroform, the product **3a** was isolated 29% and 23% yields, respectively (Table 1, entries 17 and 18). In case of toluene as a solvent, the corresponding product **3a** was isolated in 31% yield (Table 1, entry 19). Combination of two solvents like CH_3CN and EtOAc (1:1) were employed on reaction of **1a** with **2a**. In this case 80% of product **3a** was isolated (Table 1, entry 20). These experimental evidences indicate that acetonitrile solvent is required in this transformation to achieve product in good yields. The lower yields of product in the presence of various catalysts examined in Table 1 could be attributed to the possible interaction of the catalysts with the substrate. This catalyst substrate interaction may be leading to the possible competing side reaction and thereby causing decomposition of the substrate and decreasing product yield.[11]

The structure of the product **3a** was further characterised by single crystal X-ray analysis (Figure 2).

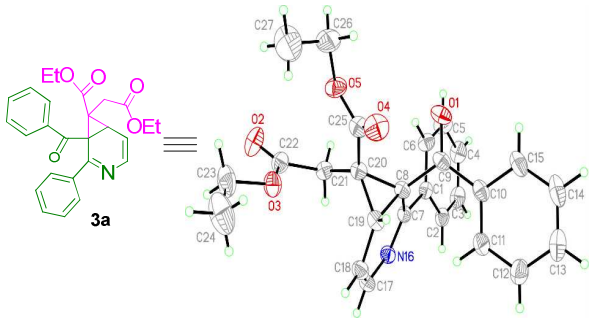
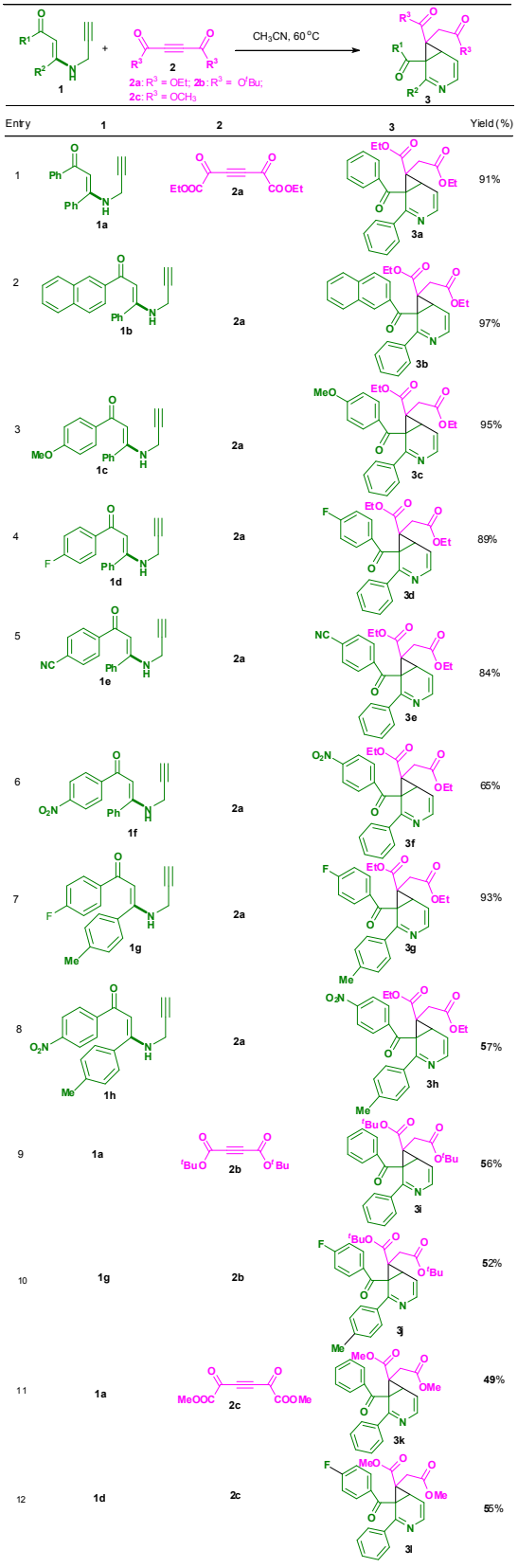


Figure 2 ORTEP representation of 3-azabicyclo[4.1.0]hepta-2,4-diene (**3a**: CCDC 932647)

Table 2 Substrate scope of 3-Azabicyclo[4.1.0]hepta-2,4-dienes



Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), CH_3CN (3 mL); All reactions were conducted under nitrogen atmosphere.

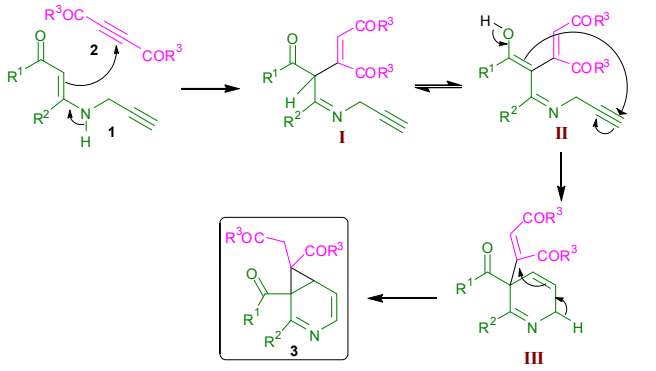
The advantage of this metal free condition is the generation of cyclopropane fused pyridine system with three contiguous stereocenters while two stereocenters are quaternary in nature.

Based on the best optimized reaction conditions (Table 1, entry 9), various substituted *N*-propargylic *β*-enaminones **1a-h** and different substituted acetylenedicarboxylates **2a-c** were employed. The results are summarized in Table 2.

When substrate **1b** reacted with **2a**, excellent yield (97%) of **3b** was isolated (Table 2, entry 2). Substrate which is having electron donating group like **1c** reacted with **2a** to give 95% yield of **3c** (Table 2, entry 3). Electron withdrawing substrates **1d**, **1e** and **1f** reacted with **2a** to give 89%, 84%, and 65% yields of **3d, 3e** and **3f**, respectively (Table 2, entries 4, 5 and 6).

N-Propargylic *β*-enaminones that contain both electron withdrawing and donating groups like **1g** and **1h** reacted with **2a** to give 93% and 57% of yields **3g** and **3h**, respectively (Table 2, entries 7 and 8). In the case of **2b** reaction with **1a, 1g** gave 56% and 52% yields of **3i** and **3j**, respectively (Table 2, entries 9 and 10). Reaction of **2c** with substrate **1a** and **1d** gave 49% and 55% yields of **3k** and **3l**, respectively (Table 2, entries 11 and 12).

A Possible reaction mechanism may be explained for the formation of fused product 3-azabicyclo[4.1.0]hepta-2,4-diene **3** from *N*-propargylic *β*-enaminone **1** and acetylenedicarboxylate **2** in Scheme 1.



Scheme 1 A possible reaction mechanism

The nucleophilic addition of *β*-enaminones **1** to the electrophile **2** would take place first to give intermediate **I**.[8f] The enolate **II** of intermediate **I** would add onto propargylic group to give cyclic intermediate **III**. Then the intermediate **III** would further undergo cyclopropanation to give cyclopropane fused dihydropyridine system **3**.

Cyclopropyl group containing molecules[12] as structural motifs are important synthetic intermediates and they exhibit potential biologically activity.[13] It may be noted that cyclopropane fused dihydropyridine systems like 3-azabicyclo[4.1.0] derivatives[14] have been reported as potent and selective triple reuptake inhibitors.[15] It would be interesting to study the biological properties of the newly synthesized 3-azabicyclo[4.1.0]hepta-2,4-dienes which are easily accessible using the present synthetic method.

In conclusion, we have developed a straight forward and efficient one pot synthesis of 3-azabicyclo[4.1.0]hepta-2,4-dienes, a cyclopropane fused pyridine system, with good to excellent yields. More significantly, this new class of 3-azabicyclo [4.1.0]hepta-2,4-diene molecules were generated with three stereocenters in a single step without using any catalyst or base. Current research is focused further exploitation of reactivity of substituted *β*-enaminone derivatives.

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