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An Unprecedented Organocascade Synthesis of Functionalized Bicyclic Nitrones from 2-Aminomalonate Derived Nucleophiles and 1-Nitro-1,3-Enynes via Allenes Formation and Subsequent Rearrangement

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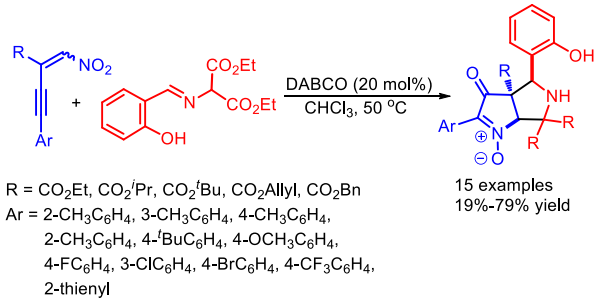
Abstract. An efficient organocatalytic cascade reaction for synthesising functionalized bicyclic nitrones is reported. The reaction of dielectrophilic ethyl 2-(nitromethylene)-4-arylbut-3-ynoate and (*E*)-diethyl 2-((2-hydroxybenzylidene)-amino)malonates to give a unique nitrone scaffold in the presence of a catalytic amount of DABCO is described. The working mechanism was proposed to proceed with allene formation followed by intramolecular cyclization and the rearrangement of an oxygen atom in the nitro group. A broad range of substrates was accessed in this facile chemical transformation, in which the bicyclic nitrones were isolated in moderate to good yields (19% to 79%) with excellent diastereoselectivity (>20:1 dr).



Keywords:, 1-Nitro-1,3-Enynes, Allene, Rearrangement, Bicyclic nitrones

Introduction

Nitrogen-containing substances are of significant importance in organic synthesis because these compounds are valuable intermediates in the synthesis of diverse naturally occurring complex molecules and potential medicinal applications.[1,2] Distinct among these functional groups, the nitrone group has served as an essential moiety in the synthesis of nitrogenous heterocycles and has demonstrated its synthetic utility, including for 1,3-dipolar cycloadditions.[3] Although various approaches have been established for synthesising nitrones under both metal-mediated[4] and metal-free[5] reaction conditions starting from secondary amines,[6] hydroxyamines,[7] imines,[8] oximes,[9] nitroalkanes,[10] etc., general strategies remain elusive. On the other hand, the development of organocascade reactions has emerged as an efficient organic synthetic strategy to construct complex chemical scaffolds.[11] The use of conjugate nitro-1,3-enynes and related derivatives in this protocol has received much attention in recent years, including 2-nitro-1,3-enynes (**1**),[12] 1-nitro-1,3-enynes (**2**)[13] and alkyne-tethered nitroalkenes (**3**).[14] Numerous chemical scaffolds that include nitrochromans (Xu),[12a] pyrano-annulated derivatives

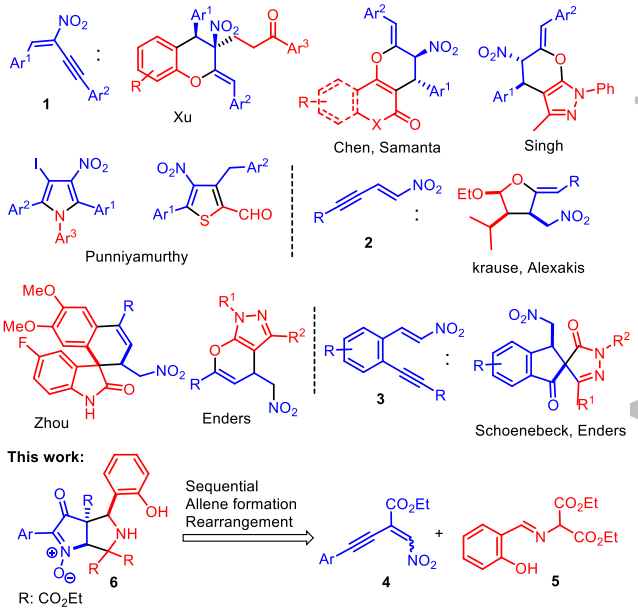


Figure 1. Structures of various nitroenynes **1-4** and their synthetic applications.

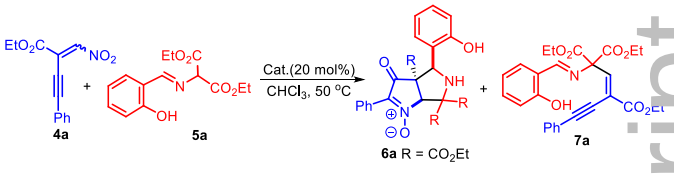
(Chen,[12b,c] Samanta,[12d] Singh[12e]), substituted pyrrole/thiophenes (Punniyamurthy),[12f-h] tetrahydrofuranyl ethers (Krause, Alexakis),[13a] spirooxindole (Zhou),[13b] pyrano-annulated pyrazoles (Enders),[13c] and spiropyrazolones (Schoenebeck, Enders)[14] were prepared using these electron deficient enynes under either organocatalytic reaction conditions or sequential organocatalysis and metal catalysis (Figure 1).

In continuation of our efforts on organocatalytic reactions on electron deficient alkynes,[12b-c, 15], herein, we report an unprecedented example for synthesis of functionalized bicyclic nitrones **6** from dielectrophilic ethyl 2-(nitromethylene)-4-arylbut-3-ynoate **4** and 2-aminomalonate derived (*E*)-diethyl 2-((2-hydroxybenzylidene)amino)malonates **5**. The organocascade process was believed to proceed *via* conjugate addition, *in situ* generation of allenes[16] and subsequent rearrangement.[17]

Results and Discussion

We initiated the study by using ethyl 2-(nitromethylene)-4-phenylbut-3-ynoate (**4a**)[18] and (*E*)-diethyl 2-((2-hydroxy-benzylidene)amino)malon ates **5a** in the presence of a Brønsted base (DABCO: 1,4-diazabicyclo[2.2.2]octane). The reaction was carried out to yield two products at ambient temperature in $CHCl_3$. The minor product was identified as an imine derived enyne **7a**, while the major product was characterized as a unique scaffold of hexahydropyrrolo[3,4-*b*]pyrrole 1-oxide **6a** (Table 1, entry 1). The chemical structures of both products were initially assigned by ^{1}H-NMR, ^{13}C-NMR and HRMS analyses.[19] The unique chemical structure of the nitrone product **6a** is intriguing, as the reaction proceeded with multi-transformations. To improve the chemical outcome of this transformation, we tried to examine the reaction temperature factor, which was gradually increased from 30 to 50 °C (Table 1, entries 2-4). Fortunately, we were able to minimize the formation of side product **7a** (9% yield) at higher reaction temperature (50 °C). Furthermore, the yield of five-membered bicyclic pyrrole scaffold **6a** was also increased to 58% (Table 1, entry 4). Then, we turned our attention to screen the utility of various Brønsted bases in the reaction. The amine base, *N*-methyl morpholine (*N*-MM) has afforded inferior result as the desired product **6a** was observed only in 12% yield, besides addition/elimination product **7a** in 30% yield (Table 1, entry 5). Other organic bases including imidazole, DMAP, Et_3N, DIPEA, and DBU failed to provide the desired product **6a**, and the production of **7a** was dominated instead. Based on these results, we made an attempt to improve the yield of **6a** by optimizing the reaction solvent. Other chlorinated solvents, such as CH_2Cl_2 and CCl_4 failed to improve the chemical yield of **6a**, and the yields were dropped to 28% and 11%, respectively (Table 1, entries 6 and 7). The applicability of nonpolar solvents such as toluene were evaluated, and only a 19% yield of **6a** was achieved (Table 1, entry 8). Presumably, this could be attributed to the lack of formation and stabilization of zwitterionic product **6a** in nonpolar solvents than it is in polar solvents. Etherated solvents, such as 1,4-dioxane and THF were not suitable for this reaction as they provide **6a** with only in 24% and 18% yield, respectively (Table 1, entries 9 and 10). Then, polar solvents such as ethyl acetate (EA) and acetonitrile were investigated; unfortunately, the low yields of products **6a** and **7a** were revealed (Table1, entries 11 and 12).

Table 1. Screening of temperature, organocatalyst and solvent in organocascade synthesis[a]



entry	cat.	temp. (°C)	Solvent	**6a** Yield [%][b]	**7a** Yield [%][b,c]
1	DABCO	rt (18.1)	$CHCl_3$	53	17
2	DABCO	30	$CHCl_3$	42	14
3	DABCO	40	$CHCl_3$	57	12
4	DABCO	50	$CHCl_3$	58	9
5	*N*-MM	50	$CHCl_3$	12	30
6	DABCO	50	CH_2Cl_2	28	9
7	DABCO	50	CCl_4	11	31
8	DABCO	50	Toluene	19	20
9	DABCO	50	1,4-dioxane	24	9
10	DABCO	50	THF	18	19
11	DABCO	50	EA	17	18
12	DABCO	50	CH_3CN	16	12

[a]To a stirred solution of diethyl (2-(2-hydroxyphenyl(imino))malonate **5a** (0.1 mmol), catalyst (20 mol%) and $CHPh_3$ (as an internal standard, 1.0 equiv.) was added enynoate **4a** slowly at 50 °C. The reaction was monitored by TLC, after enynoate **4a** was fully consumed, the reaction was quenched with H_2O.

[b]Isolated yield.

[c]During the optimization of the reaction conditions, a side reaction product was isolated and characterized. The chemical structure of the side product was temporarily assigned (**7a**). The reaction was believed to proceed through the addition/elimination reaction.

DABCO: 1,4-Diazabicyclo[2.2.2]octane; *N*-MM: *N*-methyl morpholine; THF: Tetrahydrofuran; EA: Ethyl acetate.

To further improve the chemical yield of nitrone **6a**, the adjustment of the amount of enynoate **4a** and the catalyst was studied. In the presence of 1.5 equiv. of enynoate **4a** and DABCO (30 mol%), 64% yield of the major product **6a** was obtained along with 2% of the side product **7a** (Table 2, entry 1). Comparable results were observed when either 1.8 or 2.0 equiv. of enynoate **4a** was used (Table 2, entries 2 and 3). The maximum chemical yield of nitrone **6a** was achieved when 1.8 equiv. of nitro enyne **4a** and 20 mol% of DABCO was introduced, which minimizes the

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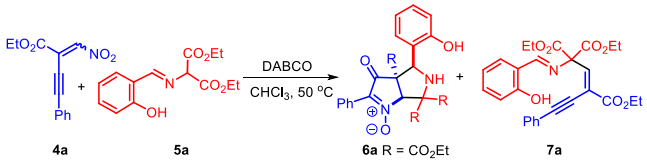
formation of addition/elimination side product **7a** (Table 2, entry 4). Next, an attempt was studied to decrease the loading of organocatalyst (10 mol% and 5 mol%), however, this led significant decrement in formation of bicyclic nitrone **6a** (Table 2, entries 5 and 6).

Table 2. Optimization of the reaction conditions[a]



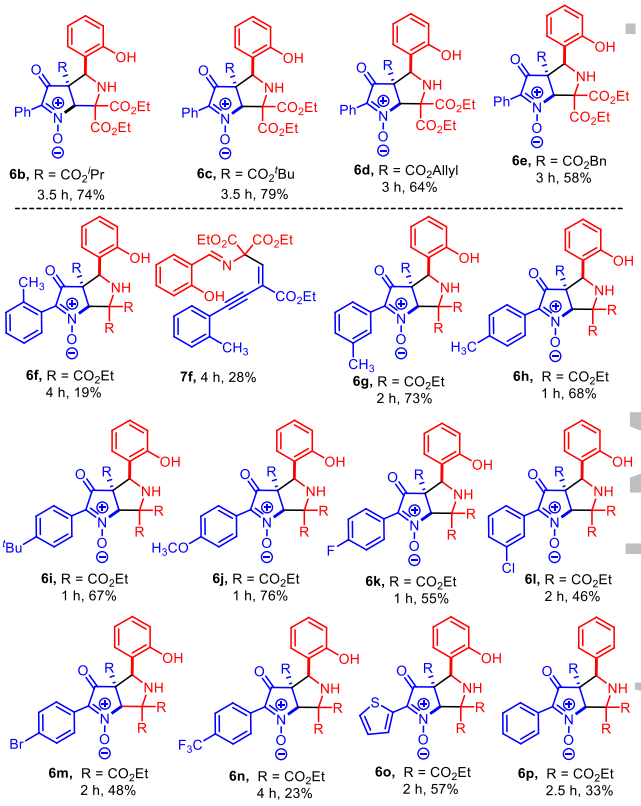
4a **5a** **6a** R = CO_2Et **7a**

entry	**4a** (equiv.)	**DABCO** (mol%)	**6a** Yield [%][b]	**7a** Yield [%][c]
1	1.5	30	64	2
2	1.8	30	68	3
3	2.0	30	62	2
4	**1.8**	**20**	**75**	**2**
5	1.8	10	54	2
6	1.8	5	40	2

[a]A solution of diethyl (2-(2-hydroxyphenyl(imino))malonate **5a** (0.10 mmol) and DABCO in $CHCl_3$ (600 µL) was slowly added to a stirred solution of enynoate **4a** in $CHCl_3$ (400 µL) at 50 °C. The reaction was monitored by crude ^{1}H-NMR, after malonate derivative **5a** was fully consumed, the reaction was quenched with H_2O.
[b]Isolated yield.
[c]Determined by crude ^{1}H-NMR using $CHPh_3$ as internal standard.
DABCO: 1,4-Diazabicyclo[2.2.2]octane

With the optimal reaction conditions in hand, we surveyed the influence of different substituents in this sequential transformation (Table 3). The chemical yields remained the same (79% to 58%) when the 2-ester group in the nitro enynoate **4** was replaced with isopropyl (**6b**), *t*-butyl (**6c**), allyl (**6d**), or benzyl (**6e**), indicating that the steric hindrance exerts limited influence on the conjunction centre of the bicyclic system. However, steric hindrance is crucial for aryl substituents in nitro enynoates **4**. The chemical yield of nitrone **6f** dropped to 19% when the 2-methyl phenyl group was present, while 28% of the addition/elimination product **7f** was also isolated. This result may be due to the significant steric repulsion between the 2-methyl group and the functionalities in close proximity. The chemical yields rebounded to 73% and 68% yield (**6g** and **6h**, respectively) when the methyl substituent was at either the *meta* or *para* position in the aryl group. Similar results were observed when the *t*-butyl and methoxy groups were examined (67% of **6i** and 76% of **6j**). The chemical yields decreased (46-55% for **6k**-**6m**) when *meta* or *para*-halo substituents were used in the aryl group of **4**. The strong electron-withdrawing group of 4-$CF_3C_6H_4$ failed to perform well in the nitrone product formation, and only a 23% yield of **6n** was obtained. The general scenario is that the electron-donating group provides better chemical yields, which is interesting in this sequential transformation. The heteroaryl substituent of thiophene was subjected to the reaction, and satisfactory results were obtained (**6o**: 57%). Finally, if the reaction was carried out in the absence of an *ortho*-hydroxy group in iminomalonate **5b** ((*E*)-diethyl 2-(benzylidene)amino)malonate), the reaction failed to proceed well and only a 33% yield of nitrone **6p** was produced (compared with that of **6a**). This result may indicate the crucial role of *ortho*-hydroxy group which increases the electrophilicity of imine through intramolecular hydrogen bonding and further facilitates the intramolecular Mannich-type cyclization (see mechanism in Scheme 1).

Table 3. Substrate scope.[a]



[a]All reactions were carried out with amino malonate derivative **5** (0.10 mmol, 1 equiv.) and enynoate **4** (0.18 mmol, 1.8 equiv.) under DABCO (20 mol%) catalysis in $CHCl_3$ at 50 °C.

We have attempted to profile a reasonable mechanism by using high resolution mass spectrometry to identify the reaction intermediates. An aliquot of the reaction mixture was taken out after 3 min and submitted for analysis. Three significant *m/z* peaks were revealed, *m/z* = 525.1872, 547.1693, and 637.2868. The ambiguous *m/z* values of 525.1872 ($[524.1795+H]^+$) and 547.1693 ($[524.1795+Na]^+$), might either come from the allene intermediate or final product because these two species have the same exact mass. The intermediate after nucleophilic attack

by DABCO was detected, with its *m/z* equals to 637.2868 (Figure 2).

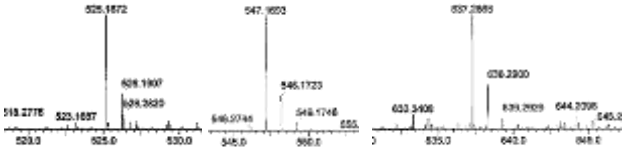
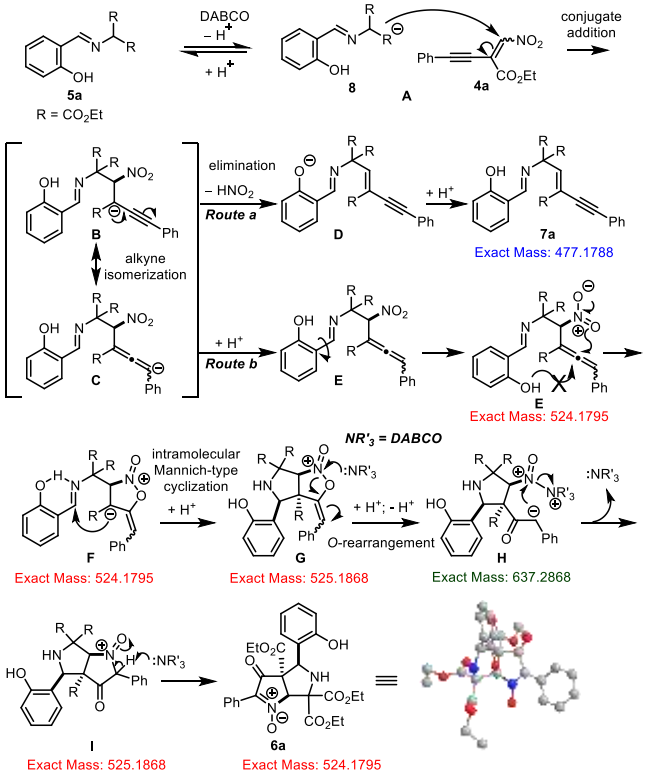


Figure 2. Intermediate identification by HRMS.



Scheme 1. Proposed reaction mechanism.

A plausible mechanism is depicted in Scheme 1. The enynoate **4a** was attacked by the deprotonated iminomalonate **8** through conjugate addition to give propargylic anion intermediate **B**, which has a resonance form of allenic anion intermediate **C**. An active allenoate **E** could be formed after facile protonation of **C** (route b).[20] The allenoate **E** would participate in favoured 5-*endo-dig* cyclization via nucleophilic addition of the proximal oxygen atom of the nitro group to give **F**, which contains a five membered-ring. A bicyclic intermediate **G** could be obtained via an intramolecular Mannich-type reaction of **F**. The bicyclic ring opening reaction could occur by the addition of DABCO to form **H,** which would be re-cyclized to give intermediate **I** (detected by HRMS). Subsequent deprotonation step to afford the bicyclic nitrone product **6**.[19] The side product **7a** was also observed in the reaction, which could be formed from intermediate **B** (route a) upon sequential elimination of one molecule of nitrous acid and protonation.

Conclusion

In conclusion, we demonstrated a feasible strategy to obtain a unique skeleton of bicyclic nitrones **6** by treatment of 1-nitro-1,3-enynes **4** with 2-aminomalonate-derived nucleophiles **5** in the presence of DABCO (20 mol%). All reactions could be completed within 4 h, and afforded the products with moderate to good yields (19-79%) with excellent diastereoselectivity. The highest yield was obtained when aryl of the enynoate **4** contains the electron-donating group. A possible mechanism for the formation of bicyclic nitrone **6** was proposed that proceed by sequential conjugate addition, alkynoate isomerization to allenoate,[21] cyclization, Mannich-type reaction, rearrangement of the oxygen atom of the nitro group, and deprotonation. Further study of related 1,3-enynes is underway in our laboratory.

Experimental Section

Diethyl (2-(2-hydroxyphenyl(imino))malonate **5** (0.10 mmol) and DABCO (20 mol%) in $CHCl_3$ (600 μL) were slowly added to a stirred solution of nitro 1,3-enynoate **4** (0.18 mol) and $CHPh_3$ (1.0 equiv.) in $CHCl_3$ (400 μL) at 50 °C. The reaction was monitored by crude ^{1}H-NMR spectrum analysis. After complete consumption of the malonate derivative **5**, the reaction was quenched with H_2O and extracted with CH_2Cl_2. The organic phases were collected, dried over $MgSO_4$ and evaporated to obtain the crude residue. The crude product was purified by flash column chromatography using EtOAC/hexanes as eluent to yield the corresponding nitrones **6**.

Acknowledgements

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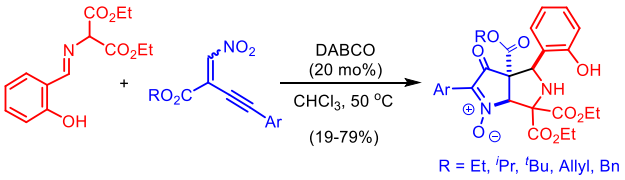
FULL PAPER

An Unprecedented Organocascade Synthesis of Functionalized Bicyclic Nitrones from 2-Aminomalonate Derived Nucleophiles and 1-Nitro-1,3-Enynes via Allenes Formation and Subsequent Rearrangement



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