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Efficient and regioselective synthesis of bicyclic pyrrolidones or bicyclic pyridones by cyclocondensation of heterocyclic ketene aminals with nitro-phenylpropiolate†

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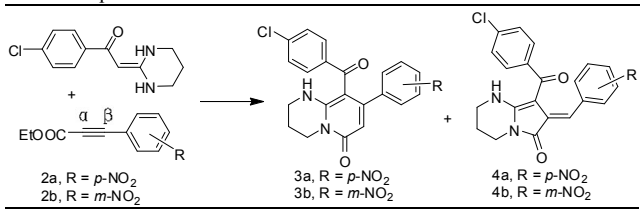
Heterocyclic ketene aminals (HKAs) underwent nucleophilic addition to the α, β-unsaturated C ≡ C of nitro-phenylpropiolate, obtaining a series of novel bicyclic pyrrolidones or bicyclic pyridones, whereas the opposite regioselectivity was observed for direct addition of HKAs to the β-C-position or α-C-position of the unsaturated ester; furthermore, this unprecedented nitro-substituted position regulated reactivity was validated by means of Density Functional Theory (DFT) calculations.

Nucleophilic addition to α, β-unsaturated carbonyl (such as acetylenic esters or alkyl propiolates) compounds has been extensively studied because it is one of the most useful methods in organic synthesis.[1] The normal Michael addition predominantly consists of conjugate addition of nucleophiles to the β-C-position of the unsaturated ester. An efficient method of addition to the α-C-position of the unsaturated ester in the presence of a phosphine catalyst (such as triphenyl phosphine) has also been reported in the literatures.[2] This two-step phosphine catalysted mechanism was initially inspired by the work of B.M. Trost et al.[3] The first step in the process involves a Michael β-C-addition of PPh_3 to alkynoate, generating an active phosphonium intermediate after proton exchange, which undergoes nucleophilic α-C-addition of the enolate followed by a H^+ transfer and elimination of PPh_3 to generate the product. Maury J. and co-workers reported radical addition with phtalimidomethyl iodide mediated by dialkylzinc can also favor regioselective addition of the radical intermediate to the α-C-position of the unsaturated ester.[4] The α-C-position and β-C-position addition of organoboronic acids by palladium catalysis to alkyl propiolates has also been reported by Chang Ho Oh and co-workers,[5] but they only obtained a mixture of the α-C-adduct and β-C-adduct products. Under catalyst-free and metal-free conditions, effective contral of regioselectivity (α-addition vs. β-addition) is essential to maximize the synthetic utility; however, it is rather difficult to accomplish. Heterocyclic ketene aminals (HKAs) are versatile bifunctional nucleophiles for the synthesis of a wide variety of fused heterocyclic compounds; many five and six membered fused heterocycles have been reported.[6] Here we report the first example of regioselective cyclocondensation of heterocyclic ketene aminals via α-C-addition or β-C-addition of a *p*-nitro-phenylpropiolate or *m*-nitro-phenylpropiolate, respectively.

The regioselective cyclocondensation of a series of HKAs with *p*-nitrophenyl propiolate or *m*-nitrophenyl propiolate were examined (**Table 1**). The reaction of 1-(4-chlorophenyl)-2-(tetrahydropyrimidin-2(1*H*)-ylidene)-ethanone **1a** with ethyl 3-(*p*-nitrophenyl) propiolate **2a** or ethyl 3-(*m*-nitrophenyl)-propiolate **2b** was first examined in a variety of solvents (such as 1,4-dioxane, THF, ethyl acetate and acetonitrile) in the presence of alkali catalysts (such as Et_3N, Cs_2CO_3, potassium tert-butoxide and piperidine). The optimal yield and regioselective cyclocondensation of bicyclic pyrrolidone **3a** or bicyclic pyridone **3b** was obtained (**Entry 10**) when a mixture of **1a** and **2b** (1.0 equiv) in acetonitrile free of alkali catalyst was heated at reflux for 6 h. The reaction did not take place in 1,4-dioxane, and gave very low yields in THF and ethyl acetate whether it contained an alkali catalyst or was catalyst-free; however, in acetonitrile if afforded the highest product yield of 84% either with an alkali catalyst or catalyst-free in several hours. Interestingly, the reaction yielded only one α-C-adduct or β-C-adduct in acetonitrile. The cyclocondensation of **1a** with ethyl 3-(*p*-nitrophenyl) propiolate **2a** in acetonitrile afforded only the α-C-adduct **4a** (bicyclic pyrrolidone) with good yield, and the β-C-adduct **3b** (bicyclic pyridone) was prepared from **1a** with ethyl 3-(*m*-nitrophenyl)propiolate (**2b**) under the same conditions.

Table 1 Optimization of the reaction conditions



2a, R = *p*-NO_2
2b, R = *m*-NO_2

3a, R = *p*-NO_2
3b, R = *m*-NO_2

4a, R = *p*-NO_2
4b, R = *m*-NO_2

Entry	**2**	Solvent	Catalyst	*t* (°C)	Time (h)	Yield
1	**2b**	dioxane	—	reflux	24	NR
2	**2b**	dioxane	Et_3N	reflux	24	NR
3	**2b**	dioxane	Cs_2CO_3	reflux	24	NR

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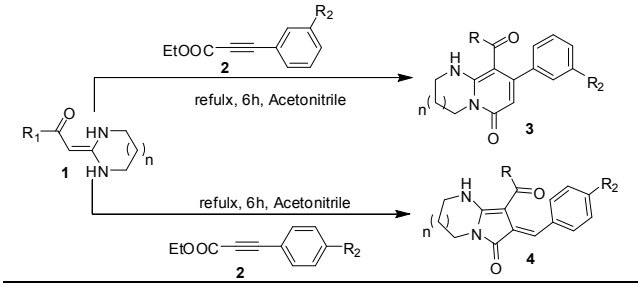
4	**2b**	dioxane	$(CH_3)_3COK$	reflux	24	NR
5	**2b**	dioxane	Piperidine	reflux	24	NR
6	**2b**	EtOAc	—	reflux	24	<5%
7	**2b**	EtOAc	Et_3N	reflux	24	<5%
8	**2b**	THF	—	reflux	24	(**3b**)13%
9	**2b**	THF	Et_3N	reflux	24	(**3b**)10%
10	**2b**	CH_3CN	—	reflux	6	(**3b**)84%
11	**2b**	CH_3CN	Et_3N	reflux	6	(**3b**)82%
12	**2b**	CH_3CN	Cs_2CO_3	reflux	6	(**3b**)78%
13	**2b**	CH_3CN	$(CH_3)_3COK$	reflux	6	(**3b**)64%
14	**2a**	CH_3CN	—	reflux	6	(**4a**)79%
15	**2a**	CH_3CN	Et_3N	reflux	6	(**4a**)80%
16	**2a**	dioxane	—	reflux	6	NR

To study the preparative scope of the new methodology, a series of HKAs (**1c-1q**) were systematically varied. (**Table 2**). A nitro-substituted position led to exclusively regioselective generation of bicyclic pyrrolidones or bicyclic pyridone products, and excellent yields were achieved within a few hours.

Table 2 Regioselective synthesis of bicyclic pyrrolidones or bicyclic pyridones



Entry	1	n	2	R_2	Yield
1	(**1c**) R_1 = 4-FC_6H_4	1	**2b**	NO_2	(**3c**) 91%
2	(**1d**) R_1 = C_6H_5	1	**2b**	NO_2	(**3d**) 82%
3	(**1e**) R_1 = 4-$CH_3C_6H_4$	1	**2b**	NO_2	(**3e**) 84%
4	(**1f**) R_1 = 4-$CH_3OC_6H_4$	1	**2b**	NO_2	(**3f**) 85%
5	(**1g**) R_1 = 2-ClC_6H_4	1	**2b**	NO_2	(**3g**) 88%
6	(**1h**) R_1 = 4-FC_6H_4	2	**2b**	NO_2	(**3h**) 75%
7	(**1i**) R_1 = 4-ClC_6H_4	2	**2b**	NO_2	(**3i**) 74%
8	(**1j**) R_1 = C_6H_5	2	**2b**	NO_2	(**3j**) 70%
9	(**1k**) R_1 = 4-$CH_3C_6H_4$	2	**2b**	NO_2	(**3k**) 71%
10	(**1l**) R_1 = 4-$CH_3OC_6H_4$	2	**2b**	NO_2	(**3l**) 72%
11	(**1c**) R_1 = 4-FC_6H_4	1	**2a**	NO_2	(**4c**) 85%
12	(**1e**) R_1 = 4-$CH_3C_6H_4$	1	**2a**	NO_2	(**4e**) 82%
13	(**1h**) R_1 = 4-FC_6H_4	2	**2a**	NO_2	(**4h**) 74%
14	(**1i**) R_1 = 4-ClC_6H_4	2	**2a**	NO_2	(**4i**) 73%
15	(**1k**) R_1 = 4-$CH_3C_6H_4$	2	**2a**	NO_2	(**4k**) 70%
16	(**1l**) R_1 = 4-$CH_3OC_6H_4$	2	**2a**	NO_2	(**4l**) 72%
17	(**1m**) R_1 = 4-FC_6H_4	0	**2a**	NO_2	(**4m**) 75%
18	(**1n**) R_1 = 4-FC_6H_4	0	**2a**	NO_2	(**4n**) 75%
19	(**1o**) R_1 = C_6H_5	0	**2a**	NO_2	(**4o**) 70%
20	(**1p**) R_1 = 4-$CH_3C_6H_4$	0	**2a**	NO_2	(**4p**) 71%
21	(**1q**) R_1 = 4-$CH_3OC_6H_4$	0	**2a**	NO_2	(**4q**) 73%
22	(**1q**) R_1 = 4-$CH_3OC_6H_4$	0	**2c**	CN	(**3r**) 89%
23	(**1q**) R_1 = 4-$CH_3OC_6H_4$	0	**2d**	F	(**3s**) 87%

From **Table 2**, the ring size of the amino group and the substituted phenyl group of HKA had a slight influence on the reactivity and product yield. Electron-withdrawing groups (such as, F and Cl) usually gave better yields (**Table 2**, entries 1 and 5). This may be due to the electron-withdrawing groups increasing the polarization of the C=C leading to increased electron density on the α-carbon of the caronyl group, making it a better nucleophile. In addition, six-member HKAs gave better yields than five-member or seven-member HKAs (Table 2, entries 11 to 21). We believe that the six-member HKAs were easier to react with nitro-phenylpropiolate. It is encouraging to note that different ethyl 3-(EWG-phenyl) propionate (such as EWG is 3-CN or 3-F, Table **2**, entries 22 to 23) can also react with HKA **1q** to get correspondent bicyclic pyridones **3r** or **3s**, respectively.

To verify the structures of the bicyclic pyrrolidones and bicyclic pyridones derivatives, **3c** and **4i** were selected as representative compounds and characterized by X-ray crystallography (CCDC 978904,979050, **Fig. 1**).

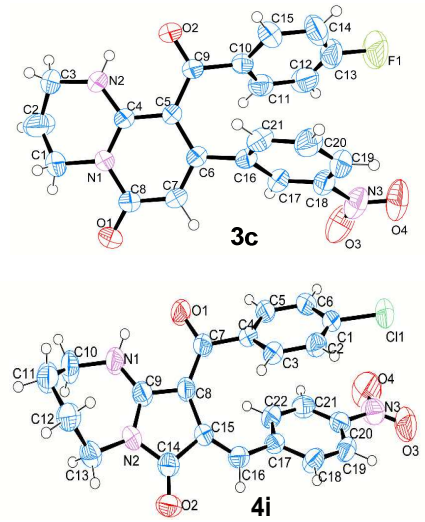
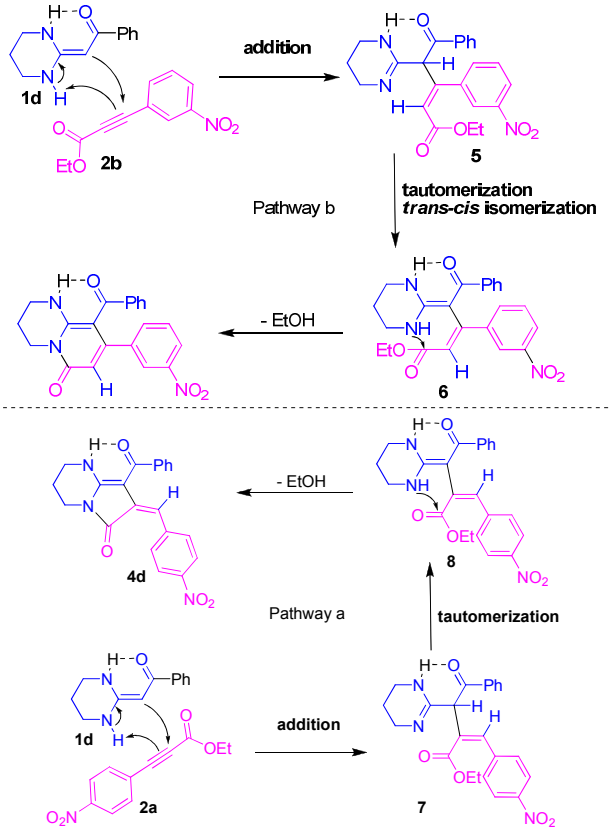


Fig. 1 X-ray crystal structures of **3c** and **4i**;[7] ellipsoids are draw at 30% probability level.

In our proposed mechanism (**Scheme 1**), the α-*C* of the ketene *N*,*N*-acetal **1d** added to the β-*C* of *m*-nitro-phenylpropiolate **2b** to afford **5**. The intermediate **5** was followed by imine-enamine tautomerization and *trans-cis* isomerization to produce **6**. Subsequently, the NH attacked the intramolecular carbonyl group and elimination of EtOH resulted in the target bicyclic pyridone **3d**. In contrast, the α-*C* of the ketene *N*,*N*-acetal **1d** added to the α-*C* of *p*-nitro-phenylpropiolate **2a** to afford **7**. The intermediate **7** was followed by imine-enamine tautomerization to produce **8**. Subsequently, it reacted in the same way to obtain the target bicyclic pyrrolidone **4d**.



Scheme 1

In order to propose a rationale for these observations, theoretical calculations were performed to further rationalize the unprecedented regioselective cyclocondensation of HKAs with nitro-phenylpropiolate. First, due to the importance of orbital factors in such reactions, the energies of the frontier orbitals of all reactants in the different solvents were calculated at the B3LYP/6-31++G(d,p)[8] level of theory (vibrational frequencies were calculated at the same level of theory to ensure that the obtained geometries were minimal). Natural bond orbital (NBO) calculations were used to visualize the molecular orbitals with the Gaussian 03 program package.[9]

Table 3. Relative energies of the frontier orbitals of HKAs (**1d**) and nitro-phenylpropiolate (**2a** and **2b**) in different solvents.

	THF	acetonitrile	dioxane
LUMO(**2a**)	-2.303	-3.011	-2.986
LUMO(**2b**)	-2.065	-2.777	-2.737
HOMO(**1d**)	-5.247	-5.277	-6.217
Δ inter (**2a-1d**)	2.944	2.266	3.231
Δ inter (**2b-1d**)	3.182	2.500	3.480

The energy diagram shown in **Table 3** enables qualitative comments on how orbital interactions influence reactivity in different solvents. The energy gaps between the HOMO (**1d**) and the LUMO of **2a** and **2b** are 3.231 eV and 3.480 eV in 1,4-dioxane, respectively, and 2.944 eV and 3.182 eV in THF. All the interactions are therefore weak and provide little driving force for the addtion of **1d** to **2a** or **2b**. In comparison, the energy gaps between the HOMO (**1d**) of the HKA and the LUMO of **2a** and **2b** are 2.266 eV and 2.500 eV in acetonitrile.

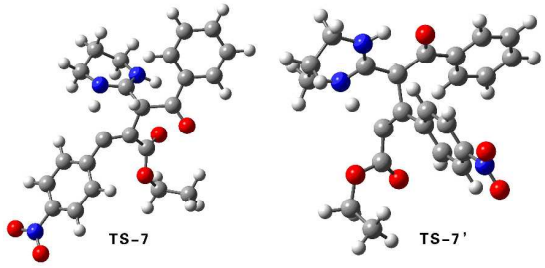


Fig. 2 Optimized transition state structure. **TS-7**: **1d** added to α-C of **2a**; **TS-7'**: **1d** added to β-C of **2a.**

This means that the HOMO-LUMO interaction should govern the reactivity and accelerate the addition of **1d** to **2a** or **2b** in acetonitrile.

In addition, full geometry optimizations of the transition states of **1d** added to **2a** or **2b** and their corresponding minima were performed. The transition state structures **TS-7** and **TS-7'** (**Fig. 2**) for HKA **1d** added to the α-*C* or β-*C* of *p*-nitro-phenylpropiolate **2a** through pathway b (**Scheme 1**), respectively, depict the H atom of the HKA transferring to the C atom of C=C in the shortest distance, similar to double bond addition reaction.[10] But the relative free energies (**Fig. 3**) of activation (⊿G) clearly indicate a preference for the attack by HKA **1d** on the α-*C* of *p*-nitro-phenylpropiolate **2a** for both TS ($\Delta G_{TS\text{-}7}$ = 56.2 kJ/mol, $\Delta G_{TS\text{-}7'}$ = 28.5 kJ/mol), affording the thermodynamically more stable product, hence confirming the experimentally observed regioselectivity of the HKA's attack on the α-*C* of *p*-nitro-phenylpropiolate **2a**. Using the same method of calculation, the relative free energies of activation indicate a preference for the attack by HKA **1d** on the β-*C* of *m*-nitro-phenylpropiolate **2b**, also confirming the experimentally observed regioselectivity of the HKA's attack on the β-*C* of the *m*-nitro-phenylpropiolate **2b** (see Supplementary data). Furthermore, NPA charges indicate that the α-*C* (NPA_{charge} = 0.139) of *p*-nitro-phenylpropiolate **2a** is considerably more positive than β-*C* (NPA_{charge} = 0.036) at the B3LYP/6-31++G(d,p) level of theory, also consistent with the experimentally observed preference.

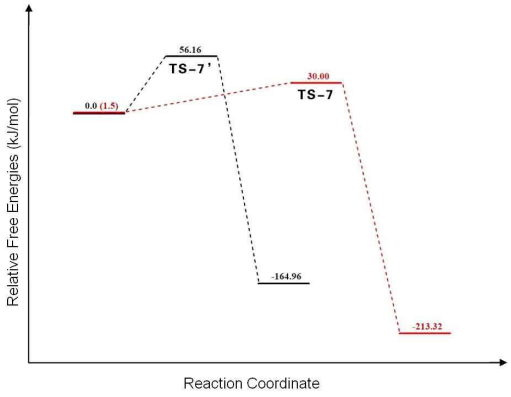


Fig. 3 Free energy profile for HKAs **1d** attack on α-C of *p*-nitrophenylpropiolate **2a** (red line); and HKAs **1d** attack on β-C of *p*-nitrophenylpropiolate **2a** (black line).

Conclusions

In conclusion, the efficient and regioselective synthesis of bicyclic pyrrolidones or bicyclic pyridones by cyclocondensation of heterocyclic ketene aminals with nitrophenylpropiolate has been described for the first time. The nitro-substituted position of phenylpropiolate can regulate the ketene *N*,*N*-acetals **1a-1q** added to the α-*C* or β-*C* of nitrophenylpropiolate (**2a** and **2b**). The observed regioselectivity was rationalized by means of orbital factors and DFT calculations, and the results described show again how the reactivity of HKA compounds can be tuned depending upon the synthetic goals. Future work will focus on analyzing more of the differences between the substituted group on phenylpropiolate responsible for the differences in regioselectivity for different HKAs' attacks on the phenylpropiolate.

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