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Alkynyl Acylammoniums as Electrophilic 3C Synthons in a Formal [3 + 3] Annulation: Access to Functionalized 4*H*-Pyran-4-ones

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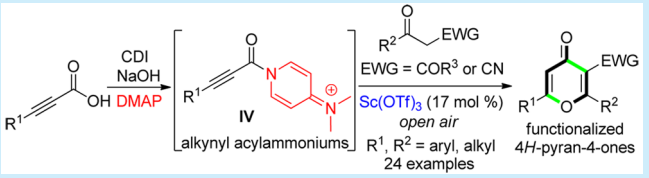
Supporting Information

ABSTRACT: Alkynyl acylammoniums generated in situ from alkynyl acids are first used as electrophilic 3C synthons in a formal [3 + 3] annulation with 1,3-dicarbonyl compounds for regioselective synthesis of functionalized 4*H*-pyran-4-ones via a 4-(dimethylamino)pyridine/Lewis acid dual-activation strategy. This protocol paves the way for further investigation of alkynyl acylammoniums as 3C synthons for construction of diverse heterocyclic skeletons.



4*H*-Pyran-4-ones (γ-pyrones) are frequently present in numerous natural products that exhibit a wide range of significant biological activities (Figure 1).[1] Moreover, they are valuable

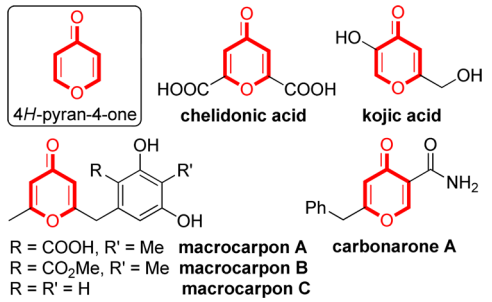


Figure 1. Representative natural products containing the 4*H*-pyran-4-one core.

building blocks for the synthesis of more complex molecules.[1c,2] Due to their remarkable biological activities and synthetic uses, a number of synthetic methods have been developed for 4*H*-pyran-4-one synthesis.[1b,h,3] Among these methods, functionalized 4*H*-pyran-4-ones are traditionally synthesized by cyclization of precursor 1,3-carbonyl compounds. However, there are more or less some limitations for these methods, including the use of expensive transition-metal catalysts and not readily accessible substrates and the narrow substrate scope. Therefore, more general and efficient synthetic approaches that allow rapid access to 4*H*-pyran-4-ones from readily accessible starting materials warrant further investigation.

The discovery of novel reactive intermediates suitable for diverse chemical transformations is critical to the field of organocatalysis. Within this area, α,β-unsaturated acylammoniums **I** derived from the combination of α,β-unsaturated acyl halides or carboxylic acids with tertiary amines have emerged as versatile electrophilic 3C synthons that can react with diverse bisnucleophiles to form cyclic compounds (Figure 2a). In 2006,

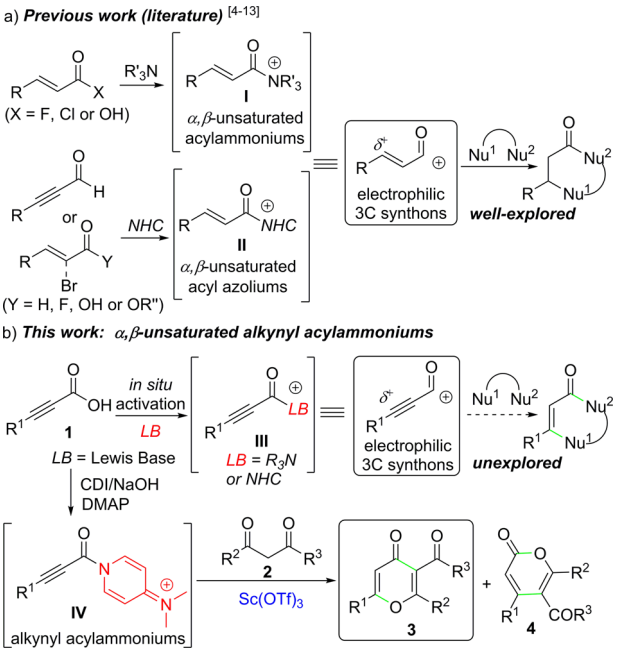


Figure 2. (a) Organocatalytic processes involving α,β-unsaturated acylammoniums and acyl azoliums; (b) alkynyl acylammoniums derived from alkynyl carboxylic acids.

Fu[4] pioneered an asymmetric formal [3 + 2] annulation of silylated indenes involving α,β-unsaturated acylammonium catalysis. Recently, Smith[5] reported isothiourea-catalyzed synthesis of dihydropyranones and dihydropyridones using mixed anhydrides as α,β-unsaturated acylammonium precursors. Moreover, Romo[6] described elegant work on asymmetric synthesis of diverse *N*- and *O*-heterocycles from acid chlorides by employing

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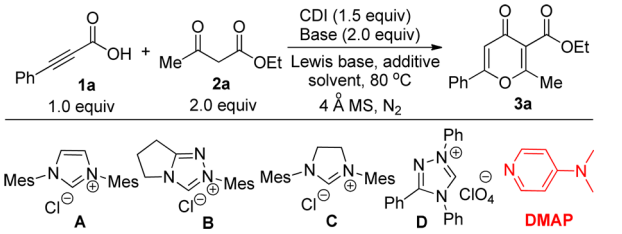
α,β-unsaturated acylammoniums. Other similar intermediates are the α,β-unsaturated acyl azoliums **II** generated from diverse precursors with N-heterocyclic carbene (NHC) catalysis,[7] including enals,[8] α- or β-bromoenals,[9] ynals,[8j,10] α,β-unsaturated acyl fluorides,[11] carboxylic acids,[12] or esters[13] (Figure 2a). Intermediates **II** have been also successfully used as versatile electrophilic 3C synthons for the synthesis of various heterocyclic compounds. Although α,β-unsaturated acylammoniums **I** and acyl azoliums **II** have been well-explored as 3C synthons for various annulations, Lewis base (a tertiary amine or an NHC)-bound alkynyl acyl intermediates **III**, to the best of our knowledge, have not been investigated as 3C synthons to undergo formal [3 + m] annulations yet (Figure 2b). We assume that intermediates **III** can be also treated as potential electrophilic 3C synthons that may display unique reactivity and thus participate in a range of chemical transformations. To test the reactivity of Lewis base-bound alkynyl acyl intermediates **III**, we envisaged a direct strategy to generate this species from readily available and more stable carboxylic acids **1** via an in situ activation strategy. Herein, we report an unprecedented, regioselective synthesis of 4*H*-pyran-4-one derivatives via DMAP (4-(dimethylamino)pyridine)/Lewis acid cooperative mediated formal [3 + 3] annulation of α,β-unsaturated alkynyl carboxylic acids with 1,3-dicarbonyl compounds, a type of commonly used 1,3-bisnucleophile (Figure 2b). By employing this method, instead of the anticipated lactones **4**, various trisubstituted 4*H*-pyran-4-one derivatives **3** were obtained in a highly regioselective manner.

In the context of our long-standing interest in NHC chemistry,[8j,k,9h,i,10d,14] our preliminary investigations began with the reaction between 3-phenylpropiolic acid (**1a**) and ethyl acetoacetate (**2a**) in the presence of several NHC precursors and carbonyldiimidazole CDI was selected as the acid-activating reagent (Table 1, entries 2−4). We found that catalytic NHC precursors **C** and **D** could promote the reaction to afford γ-pyrone **3a** in lower yields, while the reaction did not work in the absence of NHCs (entry 1). The anticipated lactone was not observed in all cases. As DMAP is frequently used as the acylation promoter via the formation of the more reactive acylammonium intermediate, we used a stoichiometric amount of DMAP to promote this reaction, and as a result, 35% of **3a** was obtained (entry 5). Considering the low cost of DMAP ($50/kg, Alibaba), we further screened a variety of solvents and bases in the presence of 1.1 equiv of DMAP (entries 6−14). Consequently, the yield was enhanced to 47% when NaOH and 1,2-DCE were employed as the base and solvent respectively (entry 14). Since Lewis base/Lewis acid cooperative catalysis[8d,14b,15] has been proved to effectively enhance both reactivity and selectivity of the reaction substrates and intermediates, we envisioned that this "dual activation" approach could improve the reaction yield in a highly regioselective mannar. Gratifyingly, after examination of three Lewis acids (entries 15−17), product **3a** was obtained in 66% yield when 17 mol % of $Sc(OTf)_3$ was employed as the additive (entry 17). We were delighted to find that the yield was not affected even if the reaction was carried out under open air (entry 18). However, attempts to lower DMAP loading led to a significantly decreased yield (entry 19). Finally, the optimal conditions were established as in entry 18.

The scope of the reaction was then investigated under the optimized conditions initially through variation of the 1,3-dicarbonyl compounds (Scheme 1). This protocol tolerates a wide range of β-keto esters including diverse acetyl or propionyl acetates and substituted benzoyl acetates. By comparison, the reaction of acetyl or propionyl acetates produced **3a−e** in lower yields, while the reaction of substituted benzoyl acetates afforded **3f−i** in higher yields. The β-diketone substrates such as acetyl acetone and 1,3-diphenylpropane-1,3-dione were also found to be applicable to this protocol despite resulting in decreased yields. However, the cyclic 1,3-diketone like cyclohexane-1,3-

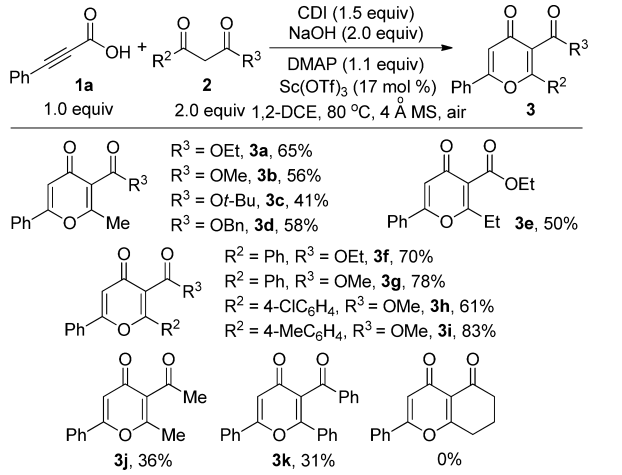
Table 1. Optimization of the Reaction Conditions[a]



entry	base	Lewis base (x mol %)	additive (17 mol %)	solvent	yield[b] (%)
1	Cs_2CO_3	none	none	1,2-DCE	<5
2	Cs_2CO_3	**A**/**B** (15)	none	1,2-DCE	<5
3	Cs_2CO_3	**C** (15)	none	1,2-DCE	21
4	Cs_2CO_3	**D** (15)	none	1,2-DCE	23
5	Cs_2CO_3	DMAP (110)	none	1,2-DCE	35
6	Cs_2CO_3	DMAP (110)	none	CH_3CN	15
7	Cs_2CO_3	DMAP (110)	none	THF	<10
8	Cs_2CO_3	DMAP (110)	none	PhMe	15
9	K_2CO_3	DMAP (110)	none	1,2-DCE	26
10	DIPEA	DMAP (110)	none	1,2-DCE	22
11	DBU	DMAP (110)	none	1,2-DCE	<10
12	Et_3N	DMAP (110)	none	1,2-DCE	25
13	LiOH	DMAP (110)	none	1,2-DCE	38
14	NaOH	DMAP (110)	none	1,2-DCE	47
15	NaOH	DMAP (110)	$La(OTf)_3$	1,2-DCE	27
16	NaOH	DMAP (110)	$Yb(OTf)_3$	1,2-DCE	41
17	NaOH	DMAP (110)	$Sc(OTf)_3$	1,2-DCE	66
18[c]	**NaOH**	**DMAP (110)**	**$Sc(OTf)_3$**	**1,2-DCE**	**65**
19[c]	NaOH	DMAP (50)	$Sc(OTf)_3$	1,2-DCE	33

[a]All reactions were performed in a 25 mL round-bottom flask on a 0.35 mmol scale with 1.0 equiv of **1a**, 2.0 equiv of **2a**, 1.5 equiv of CDI, 2.0 equiv of a base, and 200 mg of 4 Å MS (molecular sieves) in anhydrous solvent (4 mL) at 80 °C under N_2. [b]Isolated yields based on **1a**. [c]The reactions were carried out under air. Mes = 2,4,6-$(CH_3)_3C_6H_2$.

Scheme 1. Scope of the Reaction between Acid 1a and 1,3-Dicarbonyl Compounds



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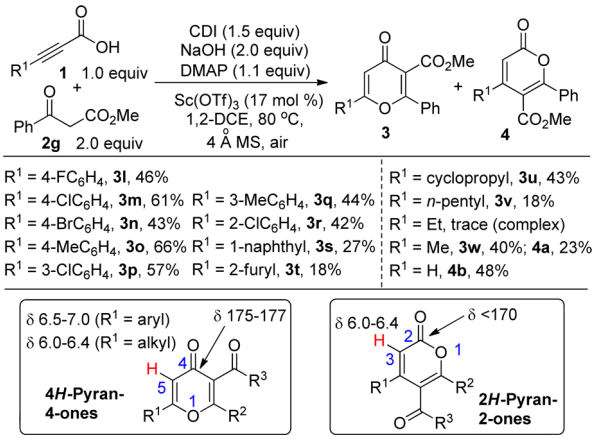
dione did not react with 3-phenylpropiolic acid **1a** under the optimized conditions.

The generality of this protocol was further probed by varying the alkynyl acid functionality (Scheme 2). A variety of substituted

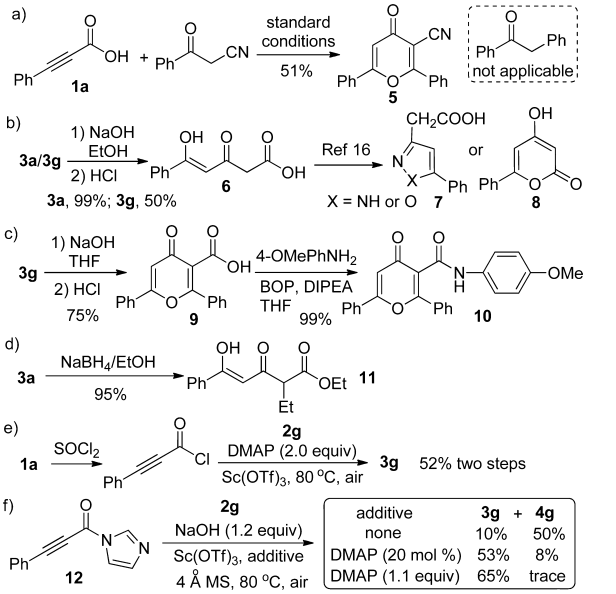
Scheme 2. Scope of the Reaction between 2g and Diverse Alkynyl Carboxylic Acids



phenylpropiolic acids reacted with methyl benzoylacetate **2g** smoothly to give the desired products **3l**−**r** in moderate yields. 3-(1-Naphthyl)propiolic acid is also suitable for this reaction, but affording product **3s** in a significantly decreased yield perhaps owing to the steric effect of 1-naphthyl group. Moreover, 3-(2-furyl)propiolic acid was found to be applicable to this protocol, but only 18% yield of product **3t** was obtained. Furthermore, several 3-aliphatic-substituted alkynyl carboxylic acids were examined to expand the breadth of this strategy. The reaction of 3-cyclopropylpropiolic acid afforded the desired product **3u** in 43% yield, while the reactions of oct-2-ynoic acid and pent-2-ynoic acid were complex, resulting in significantly decreased yields. It was also found that the reaction of but-2-ynoic acid produced 40% of pyran-4-one **3w** and 23% of pyran-2-one **4a**, while the reaction of propiolic acid exclusively gave 48% of pyran-2-one **4b**. Therefore, it is assumed that less steric hindered groups (like H) on the triple bond of the alkynyl acids **1** favored the initial conjugate addition leading to the pyran-2-ones **4**. The structures of 4*H*-pyran-4-ones **3** and 2*H*-pyran-2-ones **4** can be established by analysis of their ^{1}H and ^{13}C NMR data and are further confirmed by X-ray crystallography of **3a**. The simplest way to differentiate 4*H*-pyran-4-ones from 2*H*-pyran-2-ones is to compare the chemical shifts of the two different types of carbonyl carbons on the ring (Scheme 2). For 4*H*-pyran-4-ones, the chemical shifts of C4 are assigned between 175 and 177. For 2*H*-pyran-2-ones products, the chemical shifts of C2 are assigned below 170. The chemical shifts of the downfield protons of the pyranone cores can be also used to differentiate 4*H*-pyran-4-ones from 2*H*-pyran-2-ones in some cases. When R^1 are aryl groups, the chemical shifts of C5−H of 4*H*-pyran-4-ones are assigned between 6.5 and 7.0, while the chemical shifts of C3−H of 2*H*-pyran-2-ones are assigned between 6.0 and 6.4. However, if R^1 are alkyl groups, the chemical shifts of C5−H of 4*H*-pyran-4-ones are similar to that of C3−H of 2*H*-pyran-2-ones.

To further explore the synthetic utility of this protocol, we then focused on the application of several substrates other than 1,3-dicarbonyl compounds, as well as some chemical transformations of 4*H*-pyran-4-ones **3**. First, 2-cyano-substituted acetophenone was employed to react with **1a** under standard conditions (Scheme 3a). Gratifyingly, this reaction works smoothly to afford the desired product **5** in 51% yield. However,

Scheme 3. Synthetic Applications



2-phenyl-substituted acetophenone was found to be inapplicable to this protocol (Scheme 3a). Therefore, it may be concluded that enolizable ketones with electron-withdrawing groups at the 2-position are essential for this protocol. Subsequently, several chemical transformations of 4*H*-pyran-4-ones **3** were carried out. It was found that saponification of compounds **3a** or **3g** in different solvents resulted in different products. When **3a** or **3g** was treated with NaOH in EtOH, product **6** was obtained with loss of the acyl group (R^2CO-) after the ring-opening process (Scheme 3b). Compound **6** is an important synthetic intermediate that can be used to prepare diverse heterocyclic compounds like **7** and **8**.[16] On the other hand, saponification of **3g** with NaOH in THF afforded desired acid **9** (Scheme 3c), which is useful for the synthesis of diverse amides like compound **10**. A further application was carried out by treatment of **3a** with $NaBH_4$, and a ring-opening reductive product **11** was obtained. The ketone carbonyl was not reduced due to its conjugation with the pyrone oxygen, making it have ester character (Scheme 3d). Since alkynyl acylammoniums **IV** can be formed from acid chloride and DMAP, we carried out the reaction of **2g** with acid chloride. Consequently, 52% of **3g** was obtained within two steps (Scheme 3e). We also carried out the reaction of alkynyl acyl imidazole **12** and **2g** to get a deeper insight into the reaction process. DMAP proved to play a key role in the regioselective formation of the 4*H*-pyran-4-ones (Scheme 3f).

In summary, we have developed an unprecedented and regioselective synthesis of 4*H*-pyran-4-ones from alkynyl acids and 1,3-dicarbonyl compounds via a DMAP/Lewis acid cooperative in situ activation strategy. In this protocol, the key *α*,*β*-unsaturated alkynyl acylammoniums **IV**, to the best of our knowledge, are first applied as electrophilic 3C-synthons for a formal [3 + 3] annulation. This protocol is applicable to both 3-aromatic-substituted alkynyl acids and certain 3-aliphatic-substituted alkynyl acids. In terms of the 1,3-bisnucleophiles, electron-withdrawing groups at 2-positions of enolizable ketones are essential. We also demonstrated the utility of 4*H*-pyran-4-ones for further synthetic applications. This protocol paves the

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way for further investigation of alkynyl acylammoniums as 3C synthons for diverse [3 + *m*] annulations, which is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01891.

Experimental procedures and spectral data for all compounds (PDF)

X-ray data for compound **3a** (ZIP)

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Notes

The authors declare no competing financial interest.

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