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Base-Mediated Tandem Reaction Consisting of an Acyl Shift Strategy Leading to 4,5-Disubstiuted Furan-2(5*H*)-ones

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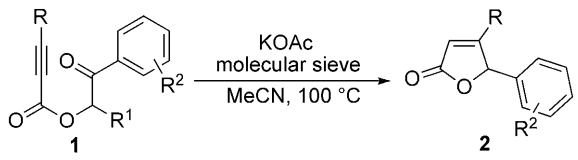
Abstract: The first example of the synthesis of 4,5-disubstiuted furan-2(5*H*)-ones by base-mediated tandem acyl shift/cyclization/decarbonylation reactions of aroylmethyl 2-alkynoates has been developed. This new and inexpensive tandem route allows both a C–O bond and a Csp^3–Csp^2 bond forming in one step involving an unprecedented acyl rearrangement process.

Keywords: acyl shift; base; C–C bond formation; cyclization; decarbonylation; furan-2(5*H*)-ones

Tandem reactions have become a powerful tool for efficient construction of important molecules from readily accessible intermediates in organic synthesis.[1] Utilization of substrates with several common functional groups, such as a C≡C bond and diverse carbonyls (ester, ketone and/or aldehyde), should make the tandem reaction much more attractive both fundamentally and synthetically because a C–O bond and a remote carbon–nucleophile bond can be formed simultaneously. Based on these substrates, the tandem synthesis of furan-2(5*H*)-ones,[2–5] important units in various natural products and biologically active compounds,[6] through a transition metal-catalyzed[3,4] or an acid-mediated process[2c,5] has been reported. However, furan-2(5*H*)-one backbones are often restricted to those methods that utilize an acid (or its derivatives) for the intramolecular oxygen-nucleophile addition with an alkyne. Therefore, the development of new valuable tandem strategies, involving a carbon-nucleophile addition process with alkynes, for preparing this class of compounds with a new structural feature ready for further elaboration is still interesting.

The acyl shift is an important method in organic chemistry,[7,8] particularly in peptide chemistry[7] and carbohydrate chemistry.[8] Despite these achievements, the acyl shift among enol esters remains less explored.[7,8] Here, we report a novel tandem route, involving an acyl shift/cyclization/decarbonylation process, to furan-2(5*H*)-ones (Scheme 1).

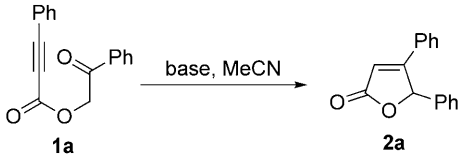
During our ongoing studies on the reaction between α-sp^3-carbons of ketones with alkynes,[9] we found an interesting transformation: 2-oxo-2-phenylethyl 3-phenylpropiolate (**1a**) underwent an unprecedented decarbonylation process with 2 equivalents of KOAc to afford 4,5-diphenylfuran-2(5*H*)-one (**2a**) in a 10% yield (entry 1, Table 1). We were pleased to find that the yield was enhanced to 46% using 4 equivalents of KOAc (entry 2), and 5 equivalents of KOAc gave the identical results (entry 3). It is noteworthy that the reaction cannot take place without bases (entry 4).[10] The results demonstrated that the reaction temperature affected the reaction (entries 2, 5 and 6). Substrate **1a** could be consumed completely at 120 °C in 5 h, affording the identical yield to that at 100 °C (entry 5). However, the activity of substrate **1a** was lowered sharply at 80 °C (entry 6). To our delight, the yield was increased to 66% in anhydrous MeCN medium, and to 70% in anhydrous MeCN combined with 4 Å molecular sieve (entries 7 and 8).



1 2

Scheme 1. Base-mediated tandem reaction consisting of an acyl shift strategy.

Table 1. Screening for reaction conditions.[a]



1a **2a**

Entry	KOAc (equiv.)	*T* [°C]	Time [h]	Isolated yield [%]
1	2	100	24	10
2	4	100	24	46
3	5	100	24	47
4	0	100	24	0
5	4	120	5	48
6	4	80	24	trace
7[b]	4	100	24	66
8[b,c]	4	100	24	70

[a] *Reaction conditions:* **1a** (0.3 mmol), base and MeCN (2 mL).
[b] In anhydrous MeCN (2 mL).
[c] 4 Å molecular sieve (200 mg).

With the optimal reaction conditions in hand, we examined the substrate scope (Table 2). It was pleasing to find that several functional groups, such as methyl, chloro, fluoro, bromo, methoxy, and nitro, on the aryl ring of the 2-oxo-2-arylethyl moiety were tolerated, but the properties of these groups affected the yields: the weakly electron-withdrawing groups (Br or Cl) afforded good yields, whereas both electron-donating and strongly electron-withdrawing groups lowered the yield (entries 1–8). While treatment of methyl-substituted substrate **1b**, for instance, with KOAc gave the target product **2b** in 56% yield (entry 1), substrate **1e** bearing a bromo group afforded 88% yield (entry 4). Although propiolate **1h** with a nitro group was consumed completely in 2 h, the yield was reduced to 48% (entry 7). Gratifyingly, substrates **1j–1m**, bearing methyl, methoxy or chloro groups on the aryl ring of the 3-arylpropiolate moiety, were also suitable for the reaction under the optimal conditions (entries 9–12). For example, substrates **1j** and **1m**,

Table 2. KOAc-mediated synthesis of furan-2(5*H*)-ones.[a]

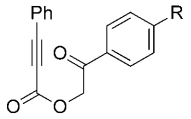
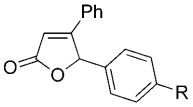
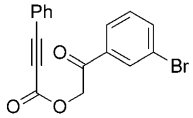
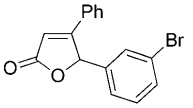
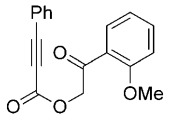
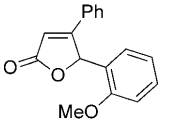
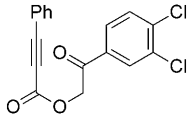
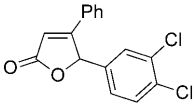
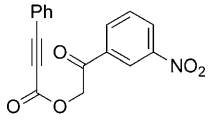
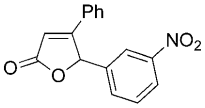
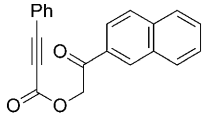
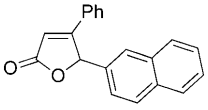
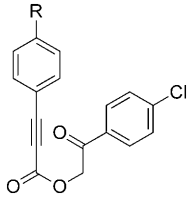
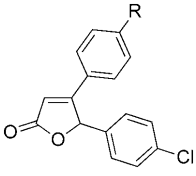
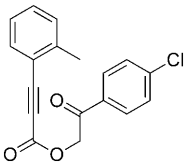
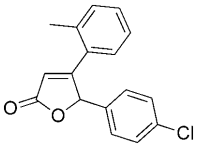
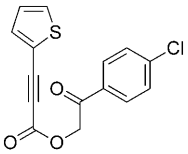
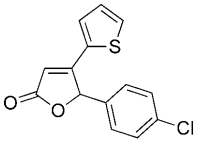
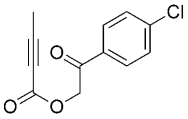
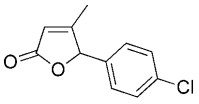
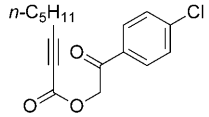
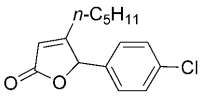
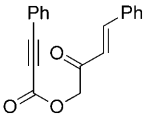
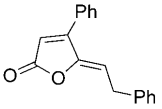
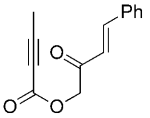
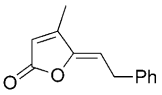
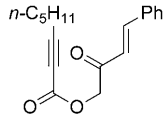
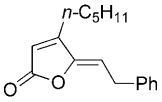
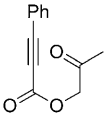
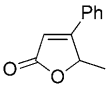
Entry	Substrate **1**		Product **2**		*t* [h]	Yield [%][b]
						
1	R = Me	**1b**	R = Me	**2b**	42	56
2	R = Cl	**1c**	R = Cl	**2c**	10	82
3	R = F	**1d**	R = F	**2d**	10	63
4		**1e**		**2e**	10	88
5		**1f**		**2f**	70	48
6		**1g**		**2g**	10	81
7		**1h**		**2h**	2	48
8		**1i**		**2i**	14	67
						

Table 2. (Continued)

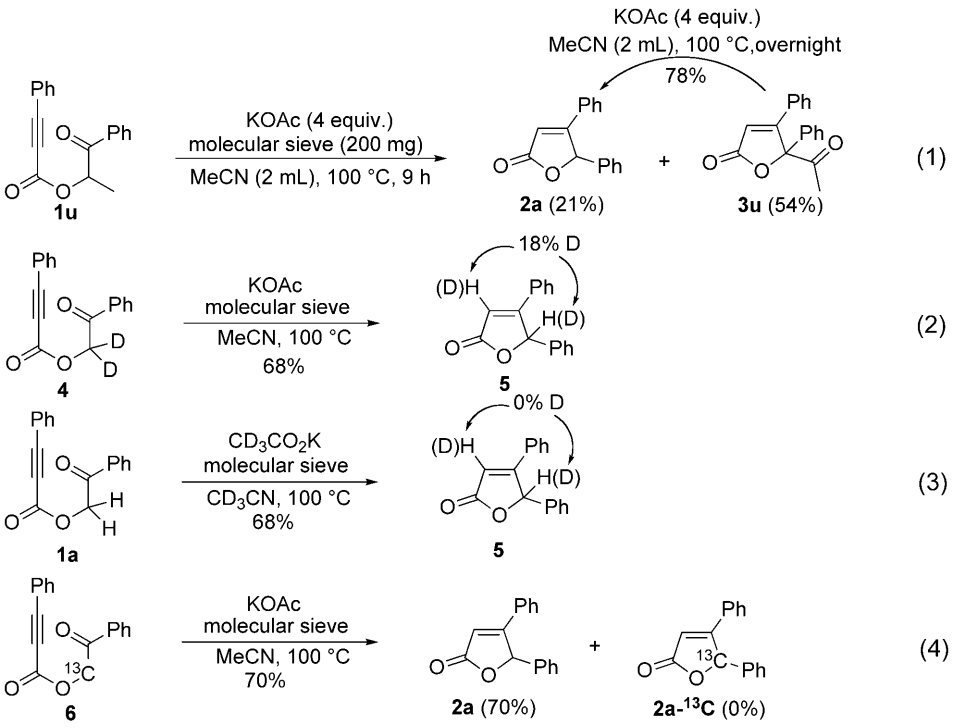
Entry	Substrate **1**		Product **2**		*t* [h]	Yield [%][b]
9	R = Me	**1j**	R = Me	**2j**	8	83
10	R = MeO	**1k**	R = MeO	**2k**	8	80
11	R = Cl	**1l**	R = Cl	**2l**	5	74
12		**1m**		**2m**	8	66
13		**1n**		**2n**	8	57
14		**1o**		**2o**	10	59
15		**1p**		**2p**	18	55
16		**1q**		**2q**	7	38
17		**1r**		**2r**	8	47
18		**1s**		**2s**	5	50
19		**1t**		**2t**	20	trace

[a] *Reaction conditions:* **1a** (0.3 mmol), anhydrous KOAc (4 equiv.), 4 Å molecular sieve (200 mg) and anhydrous MeCN (2 mL) at 100 °C.

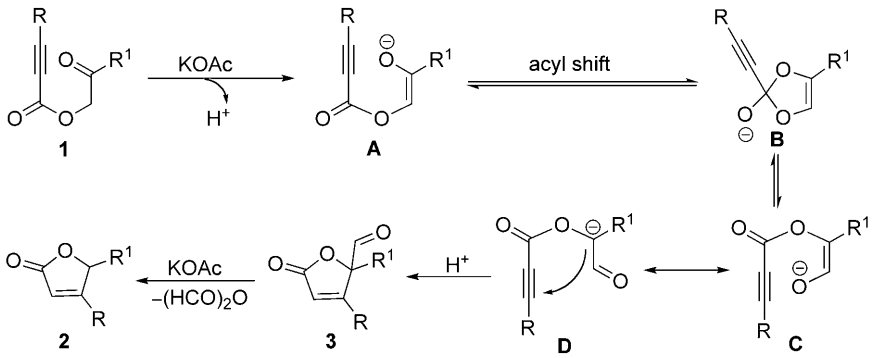
[b] Average isolated yield of two runs.

bearing a *para*- or an *ortho*-methyl group, underwent the reaction with KOAc smoothly in 83% and 66% yields, respectively (entries 9 and 12). It was noted that the reaction of thiophen-2-yl substrate **1n** was successfully run under the same conditions (entry 13). For the reactions of aliphatic alkynes **1o** or **1p**, moderate yields were still achieved (entries 14 and 15). Interestingly, vinyl ketones **1q–1s** were also suitable for the reaction resulting the corresponding (*Z*)-5-ethylidenefuran-2(5*H*)-ones **2q–2s** in moderate yields (entries 16–18). However, 2-oxopropyl 3-phenylpropiolate (**2t**) has no activity under the standard conditions (entry 19).

Notably, substrate **1u**, having a methyl group on the α-position of the carbonyl moiety, afforded two products: a cyclization/decarbonylation product **2a** and a cyclization product **3u** [Eq (1), Scheme 2]. Interestingly, product **3u** could be transferred to product **2a** under fresh basic conditions. No cross-reacted products were observed by GC-MS analysis when substrates **1a** and **1n** were simultaneously reacted with KOAc in one-pot.[11] The above results suggest that the reaction proceeds *via* an intramolecular process, and the decarbonylation step took place after the cyclization step. Both the deuterium- and ^{13}C-labeled experiments imply the occurrence of acyl shift [Eqs.



Scheme 2. Control experiments.



Scheme 3. Possible mechanism.

(2) and (4)]. Moreover, no deuterated product **5** was observed using CD_3CO_2K and CD_3CN, suggesting the transfer of the proton is not from the base and solvent [Eq. (3)]. Based on these results, we deduce that the transfer of the proton is from both substrate and water [Eqs. (2) and (3)].

Consequently, a possible mechanism was proposed as outlined in Scheme 3. Reaction of substrate **1** with KOAc affords intermediate **A**. Intermediate **A** undergoes acyl shift to yield intermediate **B**,[8] followed by cyclization to give intermediate **3**. Intermediate **3** is not stable, and undergoes the decarbonylation/protonation reaction to afford the target products **2**. We do not rule out another mechanism including the retro-Claisen-type rearrangement,[11] followed by deprotonation with base to afford intermediate **D**. Based on the mechanism, we deduce that aryl groups on the α-position of the ketone can stabilize the anionic intermediate **D** by an electron effect; however, alkyl groups without this effect result in no reaction.

The present results show that molecular sieve could improve the reaction in terms of yields. The reason may be that molecular sieve can absorb water from the reaction system and restrain hydrolysis of the alkyne.

In summary, we have described a novel method for the synthesis of furan-2(5*H*)-ones by base-mediated tandem acyl shift/cyclization/decarbonylation reactions of aroylmethyl 2-alkynoates. This novel and inexpensive tandem route allows the construction of some new bonds, including a C–O bond and a Csp^3–

Csp^2 bond, in one step. Work to extend this transformation in organic synthesis is currently underway.

Experimental Section

Typical Experimental Procedure for Base-Mediated Tandem Reaction Consisting of an Acyl Shift Strategy

A mixture of substrate **1** (0.3 mmol), anhydrous KOAc (4 equiv.), 4 Å molecular sieve (100 mg) and anhydrous MeCN (2 mL) was stirred in a Schlenk tube at 100 °C (oil bath temperature) under an argon atmosphere until complete consumption of starting material as monitored by TLC and GC-MS analysis. Then the mixture was filtered through a column, washed with diethyl ether, and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the pure product **2**.

4,5-Diphenylfuran-2(5*H*)-one (2a):[12] Yellow solid, mp 149–151 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.42 (m, 2H), 7.31–7.36 (m, 8H), 6.55 (d, J = 1.5 Hz, 1H), 6.33 (d, J = 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6, 165.8, 134.9, 131.3, 129.7 (2C), 129.2, 129.0, 127.9, 127.6, 114.7, 84.4; IR (KBr): ν = 1748 cm^{-1}; LR-MS (EI, 70 eV): *m/z* (%) = 236 (M^+, 44), 207 (15), 131 (34), 102 (100), 77 (19).

Acknowledgements

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