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A Domino Reaction of α,β-Acetylenic γ-Hydroxy Nitriles with Arenecarboxylic Acids: An Unexpected Facile Shortcut to 4-Cyano-3(2*H*)-furanones

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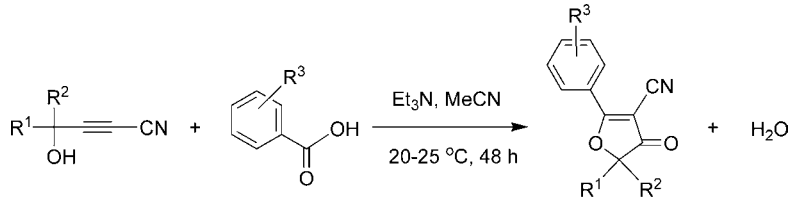
ABSTRACT



R^1, R^2 = alkyl, cycloalkyl; R^3 = H, 3-Me, 4-Me, 3-F, 2-Cl, 3-Cl, 2-Br, 3-I

An unexpected facile domino reaction of α,β-acetylenic γ-hydroxy nitriles with arenecarboxylic acids (Et_3N, MeCN, 20−25 °C, 48 h) affords 4-cyano-3(2*H*)-furanones in 67−86% yield. The reaction is triggered by the addition of an arenecarboxylic acid to a triple bond, followed by the domino reaction sequence: intramolecular transesterification−enol formation and Claisen condensation of the ketoacetonitrile tautomer with ester functional group.

The 3(2*H*)-furanone is a key structural unit in many naturally occurring compounds such as bullatenon,[1] geiparvarin,[1b,d,2] eremantholide A,[3] jatrophone,[4] and pseurotin A.[5] In addition, the 3(2*H*)-furanone derivatives are considered to be promising pharmaceutical candidates which

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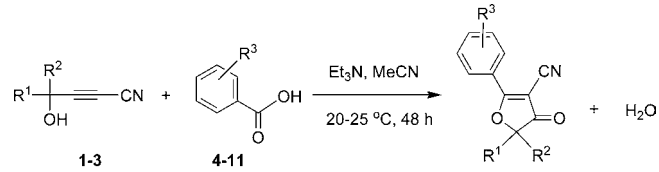
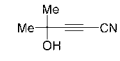
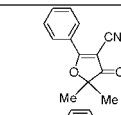
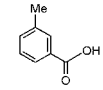
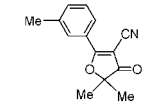
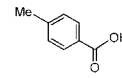
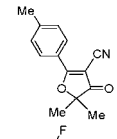
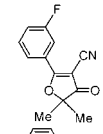
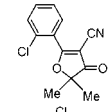
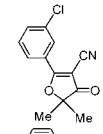
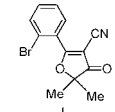
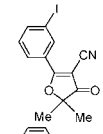
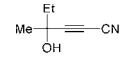
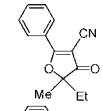
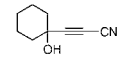
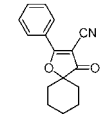
exhibit antitumor,[1b,d,2g,i,3e,6] antiulcer,[1c] antiallergic,[7] selective COX-2 inhibition,[2g,8] selective MAO-B inhibition activities,[2f,g,i,9] and ligands for nuclear hormone receptors.[10] These features have spurred growing efforts to develop more efficient syntheses of 3(2*H*)-furanones. Traditional routes to substituted 3(2*H*)-furanones utilize a cyclization/dehydration reaction of 1-hydroxy-2,4-diketones under the action of acids[2a,4b,11] or K_2CO_3.[5a] Among the alternative methods are the hydrogenolyses and subsequent acidic hydrolyses of isoxazoles,[2c,6b,12] the aldol reaction of 3-silyloxyfuranes,[13] the base-catalyzed cyclizations of 1-halo-2,4-diketones,[14] and the Knoevenagel-type condensation of α-acyloxycarbonyl compounds.[1d,15] Recently, Au(III)-, Ag(I)-, Cu(I)-, Hg(II)-, Pd(II)-, or Pt(II)-catalyzed cyclizations of propargylic ketols,[2g,16] α-hydroxy ynones,[17] and 2-oxo-3-butynoic esters or disubstituted 1,2-diones[18] to 3(2*H*)-furanones have attracted attention. More recently, the combination of (*p*-$CF_3C_6H_4)_3$PAuCl and AgOTf has been shown to actively catalyze the cyclizations of γ-hydroxyalkynones to 3(2*H*)-furanones.[2i] Still, the further development of more efficient and atom-economical routes to functionalized 3(2*H*)-furanones remains a focus of modern organic synthesis.

Herein, we report the hitherto unknown and extremely facile domino reaction between α,β-acetylenic γ-hydroxy nitriles **1**−**3** and arenecarboxylic acids **4**−**11** to deliver a novel family of functionalized 3(2*H*)-furanones, namely 5-aryl-4-cyano-2,2-dialkyl-3(2*H*)-furanones **12**−**21** in 67−86% yield. The reaction proceeds smoothly under transition-metal-free conditions at 20−25 °C in the presence of Et_3N in MeCN (Table 1).

Table 1. Synthesis of 4-Cyano-3(2*H*)-furanones[a]



1-3 4-11 12-21

	acetylene	arenecarboxylic acid	3(2*H*)-furanone	yield (%)[b]
1		**4** 	**12** 	86
	1	**5** 	**13** 	77
	1	**6** 	**14** 	80
	1	**7** 	**15** 	73
	1	**8** 	**16** 	68
	1	**9** 	**17** 	74
	1	**10** 	**18** 	67
	1	**11** 	**19** 	80
2		**4**	**20** 	74
3		**4**	**21** 	79

[a] Reaction conditions: acetylenes **1**−**3** (1 mmol), arenecarboxylic acids **4**−**11** (1 mmol), Et_3N (1 mmol), MeCN (6 mL), 20−25 °C, 48 h. [b] Isolated yield after recrystallization or preparative TLC.

The 3(2*H*)-furanones **12**−**21** are crystalline compounds with sharp melting points and good solubility in most organic solvents (examples: acetone, acetonitrile, benzene, chloroform, diethyl ether, dimethyl sulfoxide, ethanol, methanol) and poor solubility in water. In addition, the structure of

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4-cyano-2,2-dimethyl-5-phenyl-3(2*H*)-furanone **12** was confirmed by single-crystal X-ray analysis (Figure 1).

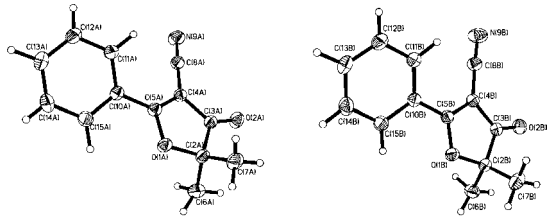
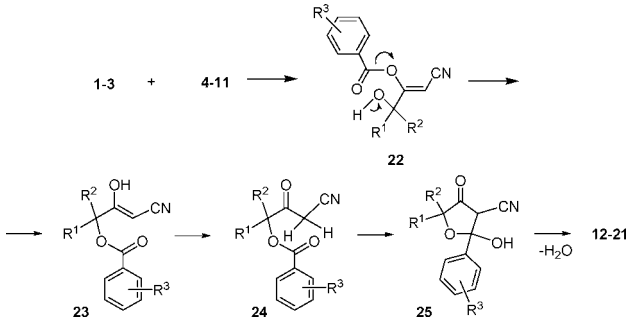


Figure 1. X-ray crystal structures of **A** and **B** molecules of **12**.

The reaction conditions and resulting products in Table 1 indicate a domino sequence that is triggered by the nucleophilic addition of arenecarboxylic acids **4**−**11** across the triple bonds of acetylenes **1**−**3** to afford the enol esters **22** (Scheme 1). The enol esters are transformed via intramolecular transesterification to the enols **23**, subsequently tautomerizing to the keto esters **24**. The latter undergo a ring closure via intramolecular Claisen condensation with participation of the active CH_2 group of the β-ketonitrile and the carbonyl function of the ester residue to give hemiketals **25**. After dehydration to form a $C_{sp2}-C_{sp2}$ bond, the 3(2*H*)-furanones **12**−**21** are produced.

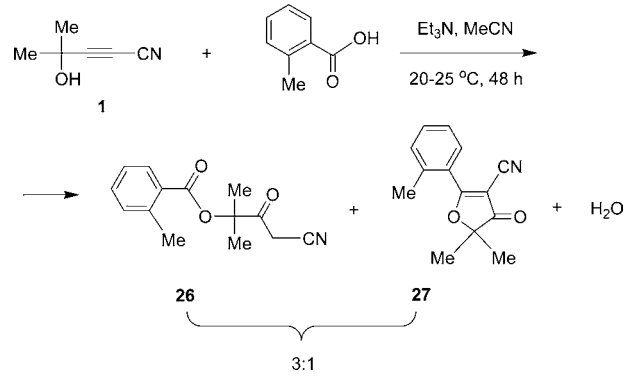
Scheme 1. Plausible Scheme of Domino Sequence Leading to 3(2*H*)-Furanones **12**−**21**



The reaction can be stopped at the stage of the intermediate keto esters **24**. For example, the keto ester **24** ($R^1 = R^2 =$ Me, $R^3 =$ H) was isolated from the reaction mixture in 31% yield, after acetylene **1** and benzenecarboxylic acid **4** were allowed to react in the presence of 10 mol % of K_2CO_3 at 20−25 °C for 48 h (the water was not specially added to the reaction mixture). When ketone **24** had been kept in acetonitrile in the presence of Et_3N at 20−25 °C (i.e., under the Table 1 reaction conditions), the expected 3(2*H*)-furanone **12** was detected (^{1}H NMR) in the reaction mixture (30% conversion after 3 h).

In addition, the keto ester **26** ($R^1 = R^2 =$ Me, $R^3 =$ 2-Me) was obtained as a mixture with 3(2*H*)-furanone **27** in a ratio of 3:1, respectively (Scheme 2).

Scheme 2. Reaction of Acetylene **1** with 2-Methylbenzenecarboxylic Acid



Keto esters similar to **26** were formed as adducts between 3- and 4-aminobenzenecarboxylic acids and α,β-acetylenic γ-hydroxy nitriles **1**−**3**.[19]

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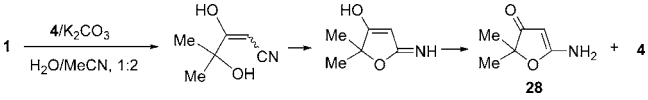
It is noteworthy that an equimolar amount of aqueous K_2CO_3 did not catalyze the addition of benzenecarboxylic acid **4** to acetylene **1** to afford 3(2*H*)-furanone **12** (water−MeCN, 1:2; 20−25 °C, 48 h). Instead, hydration of acetylene **1** to 5-amino-2,2-dimethyl-3(2*H*)-furanone **28** in a yield of 76% occurred (Scheme 3).[19,20]

Scheme 3. Synthesis of 5-Amino-2,2-dimethyl-3(2*H*)-furanone **28**

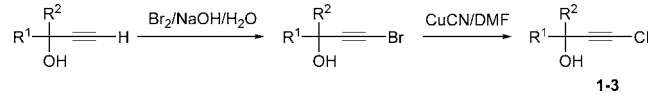


Commonly, carboxylic acids are known to add to various acetylenes[21] (terminal alkynes,[21a,c,d,f,g,i−k] propargyl alcohols and their derivatives,[21a,b,f,h,i] dimethyl acetylenedicarboxylate[21e]) under heating (60−110 °C) for 4−96 h[21] exclusively in the presence of ruthenium catalysts, mostly complexes of complicated structure. Of industrial importance remains the classic vinylation of carboxylic acids with acetylenes by the action of $HgSO_4$, $Zn(OAc)_2$/C, H_3PO_4/C, Zn/Cd, and Zn/Cd/Hg catalytic systems.[22] Also known are attempts to vinylate carboxylic acids with acetylenes over palladium.[23]

Thus, the first stage of the Scheme 1 domino reaction represents a unique example of transition-metal-free additions of carboxylic acids to carbon−carbon triple bonds. Taking into account that the starting acetylenic hydroxy nitriles **1**−**3** are readily available from acetylenic alcohols and copper cyanide through the intermediary acetylenic bromides (Scheme 4),[24] the domino assembly presented here may be considered as one of the most concise and expedient approaches so far known to functionalized 3(2*H*)-furanones.

Of special synthetic significance of this synthesis is that it allows the cyano group (which may be easily converted to amino,[25] amido,[26] or carboxylic[26a−c] functions) to be introduced into the cyclopentanone moiety. Evidently, the reaction should be of general character and be valid for various carboxylic acids and α,*β*-acetylenic *γ*-hydroxy nitriles with tertiary alcohol moieties. Certainly, the scope and limitation of the reaction is still to be further scrutinized. α,*β*-Acetylenic *γ*-hydroxy nitriles with primary and secondary alcohol moieties are poorly understood (among them only 4-hydroxy-2-butynenitrile is known[27]). Amino analogues of hydroxyacetylenes **1**−**3** are almost inaccessible: just 4-amino-2-butynenitrile has been so far described as hydrochloride.[27b] In the case of aliphatic carboxylic acids, under the conditions studied, a mixture of products containing the expected 3(2*H*)-furanones and intermediate keto esters (in ratio 1−2:1) is formed; hence, the reaction promises to be successfully optimized.

Scheme 4. Synthesis of α,*β*Acetylenic *γ*-Hydroxy Nitriles **1**−**3**



In summary, a new synthetic concept for the design of functionalized 3(2*H*)-furanones in a one-step, extremely facile domino reaction of available α,*β*-acetylenic *γ*-hydroxy nitriles and arenecarboxylic acids has been put forward and experimentally proved. The concept may find a widespread application and propagation in the synthesis of pharmaceutically important functionalized 3(2*H*)-furanones.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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