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Trialkylphosphine-Mediated Synthesis of 2-Acyl Furans from Ynenones

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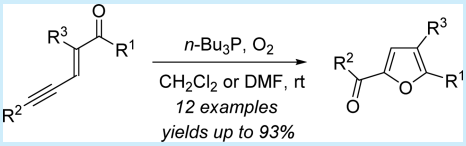
Supporting Information

ABSTRACT: A novel reaction for the synthesis of 2-acyl furans is reported. The reaction is believed to proceed by sequential addition of a trialkylphosphine to an ynenone, 5-*exo-dig* cyclization to form the furan, and oxidation of the resulting phosphonium ylide with molecular oxygen. Many common functional groups are tolerated during the reaction, and the products are obtained in good to excellent yield under the mild conditions. This methodology offers efficient access to biologically important compounds, including fused polycyclic compounds and furaldehydes, from simple starting materials.

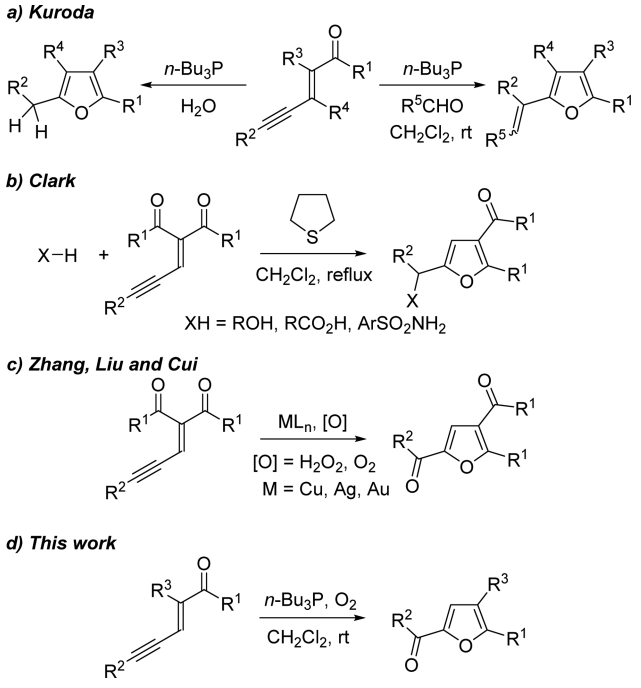


Substituted furans are ubiquitous and are often found in bioactive natural products,[1] pharmaceuticals,[2] and organic materials.[3] Furans are also valuable synthetic intermediates because they serve as masked 1,4-dicarbonyl compounds and can be transformed into a variety of other functional groups.[4] As a consequence of the importance of furan-containing systems, the development of new and more efficient methods for the synthesis of furans is of general interest to organic chemists.[5] Although there are several well-established general methods for furan synthesis,[6] metal-catalyzed reactions that employ copper,[7] zinc,[8] palladium,[9] and gold[10] complexes are becoming increasingly popular and offer several advantages in terms of efficiency and functional group compatibility when compared to traditional methods. Organocatalytic processes for the synthesis of furans have also been described, such as Krische's phosphine-mediated reductive condensation of γ-acyloxy butynoates[11] and Jørgensen's synthesis of 2-hydroxyalkyl and 2-aminoalkyl furans,[12] but these approaches have been used less frequently.

Ynenones have emerged recently as versatile starting materials for the synthesis of furans. For example, Kuroda and co-workers reported an organophosphine-induced tandem furan formation and Wittig reaction sequence (Scheme 1a).[13] Additionally, our group has discovered the tetrahydrothiophene-catalyzed synthesis of highly substituted furfuryl alcohols, amines from ynenones (Scheme 1b)[14] and a Brønsted acid promoted cascade reaction for the synthesis of cyclopropyl-substituted furans.[15] Interesting examples of transition-metal-catalyzed oxidative formation of 2-acyl furans in moderate to good yield have been published by the groups of Zhang,[16] Liu,[17] and Cui[18] (Scheme 1c). On the basis of these reports and results of prior studies concerning the synthesis of furans from ynenones, we postulated that treatment of a simple ynenone with a stoichiometric amount of a trialkylphosphine in the presence of an oxidant could deliver a functionalized 2-acyl furan (Scheme 1d).

Preliminary experiments were performed using the ynendione **1a** and the ynenone **1b** as the model substrates with

Scheme 1. Syntheses of Highly Functionalized Furans from Ynenones



oxygen as the oxidant (Table 1). Reaction conditions were varied in order to minimize the reaction time and maximize the yield. Optimization experiments revealed that the most suitable solvents for this reaction were dichloromethane and benzene; the desired product **2a** was obtained in yields of 95% and 98%, under standard conditions (entries 1 and 6). Solvents such as THF, methanol, and hexane were not effective for this transformation (entries 2−4), but DMF was suitable in some

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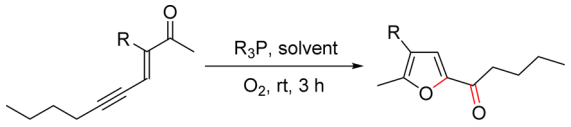
Table 1. Optimization of Reaction Conditions[a]



1a R = COMe
1b R = H

2a R = COMe
2b R = H

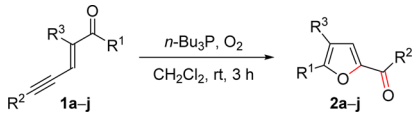
entry	substrate	solvent	initiator	conversion (%)[b]
1	**1a**	CH_2Cl_2	*n*-Bu_3P	95[c]
2	**1a**	THF	*n*-Bu_3P	–[d]
3	**1a**	hexane	*n*-Bu_3P	trace
4	**1a**	MeOH	*n*-Bu_3P	–[d]
5	**1a**	DMF	*n*-Bu_3P	80
6	**1a**	benzene	*n*-Bu_3P	98[c]
7	**1b**	benzene	*n*-Bu_3P	50[c]
8	**1a**	benzene	Ph_3P	99
9	**1b**	benzene	Ph_3P	–[d]

[a]Reaction conditions: **1** (0.1 mmol), initiator (0.2 mmol), solvent (10 mL), at rt for 3 h under a static oxygen atmosphere unless noted otherwise. [b]Conversion was determined by ^{1}H NMR analysis using trimethoxybenzene as an internal standard. [c]Isolated yield. [d]Furan **2a**/**2b** was not isolated.

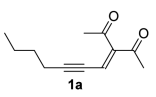
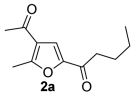
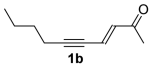
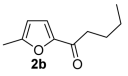
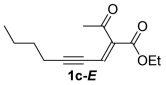
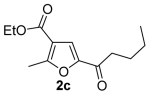
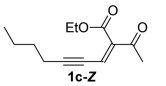
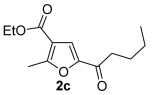
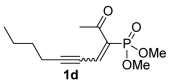
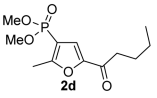
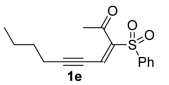
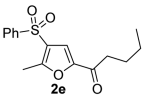
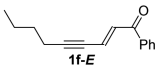
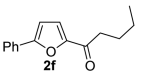
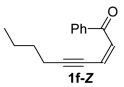
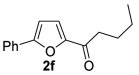
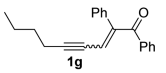
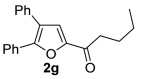
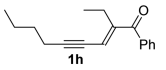
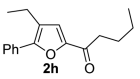
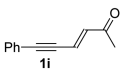
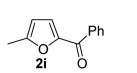
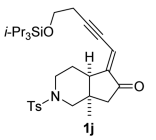
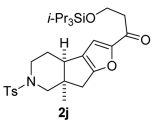
cases (entry 5). Various nucleophilic reagents were assessed for their ability to perform 2-acyl furan formation. It was found that tri-*n*-butylphosphine and triphenylphosphine both cyclized **1a** to give **2a** (entries 6 and 8). However, treatment of the less reactive ynenone **1b** with tri-*n*-butylphosphine delivered the desired furan product **2b** in moderate yield (entry 7) and only starting ynenone **1b** was recovered when triphenylphosphine was employed (entry 9). The crucial role played by phosphine was demonstrated by the fact that the 2-acyl furans **2a** and **2b** were not obtained when alternative reagents such as DABCO, DMAP, or tetrahydrothiophene were employed as nucleophilic organocatalysts.

On the basis of the results of preliminary experiments and safety considerations, dichloromethane was identified as the solvent of choice for the oxidative cyclization reactions. Structurally diverse ynenones were then synthesized and examined as substrates in the organophosphine-mediated reaction (Table 2). In most cases, the expected 2-acyl furans were obtained in moderate to excellent yields. The cyclization reaction proceeded in high yield with substrates in which R^3 is electron-withdrawing (entries 1 and 3–6), irrespective of the alkene geometry. It is notable that a reasonable yield of furan **2b** was obtained from the reaction of ynenone **1b** (entry 2), a substrate that is problematic with methods described by others.[16−18] Furthermore, high yields could be obtained in some cases where air was used as the oxidant (entry 6). Significantly, the *E* and *Z* isomers of the phenyl-substituted ynenone **1f** both reacted under standard conditions to afford furan **2f** in good yield (entries 7 and 8). However, reduced reactivity was observed when R^3 is an aryl substituent (entry 9) and the furan **2h** was not obtained in the case where R^3 is an alkyl group; the starting ynenone **1h** was recovered in this case (entry 10). The reaction was also performed on phenyl-substituted alkyne **1i**, but the furan **2i** was obtained in low yield (entry 11). It is also noteworthy that when highly functionalized starting material **1j** was subjected to the reaction conditions, the fused tricyclic furan **2j**, corresponding to the A–C fragment of the marine alkaloid nakadomarin A,[19,20] was obtained in excellent yield (entry 12). This result demonstrates that the reaction can be used to synthesize fused ring systems.[21]

Table 2. Substrate Scope for Formation of 2-Acyl Furans[a]



1a–j **2a–j**

entry	method[a]	ynenone	furan product	yield (%)[b]
1	A	 **1a**	 **2a**	71
	C			85
2	A	 **1b**	 **2b**	45
3	A	 **1c-*E***	 **2c**	90
4	A	 **1c-*Z***	 **2c**	93
5	A	 **1d**	 **2d**	59[c]
6	B	 **1e**	 **2e**	82
7	A	 **1f-*E***	 **2f**	89
8	A	 **1f-*Z***	 **2f**	89
9	A	 **1g**	 **2g**	25[d]
10	A	 **1h**	 **2h**	–[e]
11	A	 **1i**	 **2i**	27
12	C	 **1j**	 **2j**	92

[a]Reaction conditions: (A) *n*-Bu_3P (2 equiv) added to a solution of **1** in CH_2Cl_2 at rt, and the mixture stirred for 3 h under a static atmosphere of oxygen; (B) a solution of **1** in CH_2Cl_2 added to a solution of *n*-Bu_3P (1.1 equiv) in CH_2Cl_2 at rt, and the mixture stirred for 3 h under a static atmosphere of air; (C) a solution of **1** in DMF added to a solution of *n*-Bu_3P (4 equiv) in DMF at rt, and the mixture stirred for 3–8 h under a static atmosphere of oxygen. [b]Isolated yield. [c]Both *E* and *Z* isomers were consumed during the reaction. [d]The isomers of **1g** were also cyclized individually to give 15% and 26% yields of **2g**. [e]The ynenone **1h** was recovered in 60% yield.

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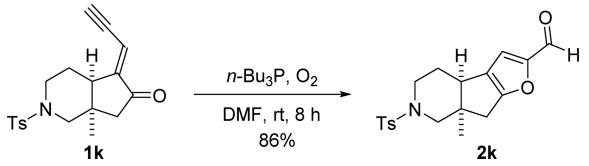
Treatment of substrate **1k**, which contains a terminal alkyne group, with tri-*n*-butylphosphine and oxygen in dichloromethane resulted in a smooth reaction to deliver the tricyclic furaldehyde **2k** in 86% yield (Scheme 2). Aldehydes of this type

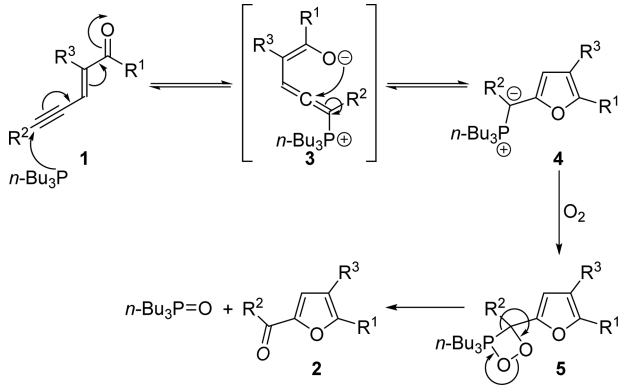
Scheme 2. Synthesis of a Polycyclic Furaldehyde



are potentially unstable, and the success of the transformation demonstrates the mildness of the reaction conditions. This result suggests that the reaction should be useful for the synthesis of synthetic intermediates or bioactive natural products that contain a sensitive 2-furaldehyde.[22]

A plausible reaction mechanism based on Kuroda's[13] previous report and our preliminary experimental studies is shown in Scheme 3. In this mechansim, tri-*n*-butylphosphine

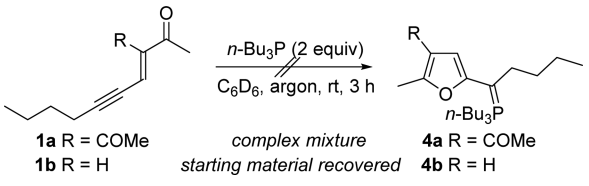
Scheme 3. Possible Reaction Mechanism



undergoes reversible 1,6-addition to the ynenone **1** to generate the zwitterion **3**. Subsequent 5-*exo*-*dig* cyclization by nucleophilic addition to the allene affords the phosphonium ylide **4**. Finally, the desired 2-acyl furan **2** is produced by reaction of the ylide **4** with oxygen, possibly via the phosphadioxetane **5**. Few examples of the direct oxidation of phosphorus ylides have been described; those would usually involve singlet oxygen,[23] a phosphite-ozone adduct,[24] or an oxaziridine.[25] To the best of our knowledge there are no literature precedents for the use of oxygen or air as the oxidant to provide the carbonyl product from a simple phosphonium ylide.

NMR experiments were performed on substrates **1a** and **1b** in an attempt to detect and identify the intermediates involved in the reaction (Scheme 4).[26] Unfortunately, treatment of **1a**

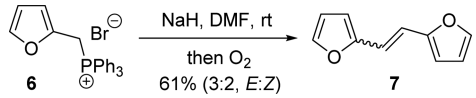
Scheme 4. Mechanistic Studies



and **1b** with an excess of tri-*n*-butylphosphine in d6-benzene under an atmosphere of argon at room temperature did not produce spectroscopically identifiable quantities of the expected intermediate phosphonium ylides **4a** and **4b**. In the case of the diketone **1a**, starting material was consumed rapidly to give a complex mixture of unidentified products and subsequent introduction of air did not deliver the expected product **2a**. In contrast, the less reactive ynenone **1b** did not undergo reaction in the absence of oxygen, but subsequent introduction of air into the reaction vessel resulted in the reaction of ynenone **1b** to give the expected furan product **2b** with a good level of conversion. Based on these observations, we proposed that 1,6-addition of the trialkyphosphine to an ynenone is favored for reactive substrates where R^3 is an electron-withdrawing group, and that an intermediate is generated, which reacts with the starting ynenone and/or degrades in the absence of oxygen. Conjugate addition of the trialkyphosphine to the less reactive substrate **1b** is unfavorable, and oxygen is required to drive the equilibrium toward 2-acyl furan **2b**. This observation suggests that an equilibrium is established in which the starting materials are favored. In neither case could significant amounts of the putative phosphonium ylide intermediate **4** or its precursor **3** be detected by ^{31}P NMR.[27]

In order to discover whether transformation of the phosphonium ylide **4** into the acyl furan **2** was possible (Scheme 3), direct oxidation of a furan-containing ylide, generated by deprotonation of a phosphonium salt, was investigated (Scheme 5). Furfuryltriphenylphosphonium bro-

Scheme 5. Reaction of a Phosphonium Ylide with Oxygen



mide (**6**)[28] was deprotonated with sodium hydride, and the resulting ylide was exposed to oxygen. This reaction delivered the alkene **7**[29] (61% yield, 3:2 mixture of *E* and *Z* isomers) resulting from oxidation of the ylide to give furfural followed by Wittig reaction of the aldehyde with unoxidized ylide. The outcome of this reaction demonstrates that a furan-containing phosphonium ylide can be oxidized with oxygen to give the corresponding aldehyde and provides evidence to support the proposed reaction mechanism (Scheme 3).

In summary, we have discovered a phosphine-mediated 2-acyl furan forming reaction that has a broad reaction scope. The simple and mild reaction employs readily available ynenones as substrates and offers a direct access to di- and trisubstituted furan derivatives including fused tricyclic acyl furans and furaldehydes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01533.

Experimental procedures plus spectroscopic and other data for compounds **1f–k** and **2a–k** (PDF)

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Notes

The authors declare no competing financial interest.

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