

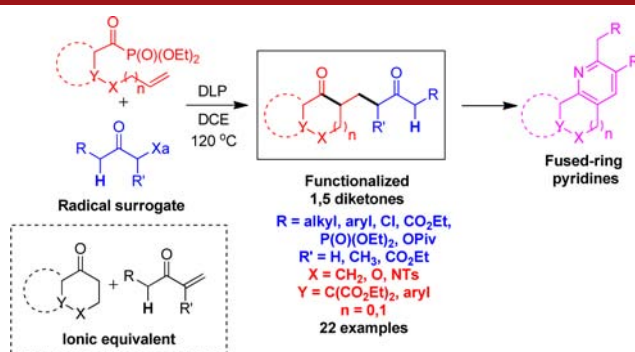
Free-Radical Variant for the Synthesis
of Functionalized 1,5-DiketonesKelvin Kau Kiat Goh,^{†‡} Sunggak Kim,^{*†} and Samir Z. Zard^{*‡}

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ABSTRACT



A free-radical approach for the synthesis of functionalized 1,5-diketones has been accomplished through an effective combination play between alkenylacylphosphonates and keto-xanthates as radical surrogates of enolates and enones, respectively.

1,5-Dicarbonyl compounds are invaluable building blocks in the synthesis of fused-ring systems that are commonly found in alkaloids, steroids, and terpenes.¹ In particular, 1,5-diketones are known to provide an easy access to functionalized pyridines.²

Classical methods to synthesize 1,5-dicarbonyl compounds generally invoke the use of enolates and methyl vinyl ketones via conjugate addition as in the Robinson annulation.³ Even so, limitations have plagued this approach owing to the nature of the requisite precursors, in particular, the easily polymerized methyl vinyl ketone, and the difficulty in controlling the reactivity of the anionic enolate.^{1a}

To address these issues, modifications centered on these starting precursors have been devised, as exemplified

by the use of silyl enol ethers in Lewis acid catalyzed Mukaiyama aldol reactions or enamine-mediated reactions⁴ and Mannich-type bases or α -silylated ketones.⁵

Nonetheless, since the synthesis remains revolved around these two starting materials as 1,5-dicarbonyl precursors and their corresponding modifications,^{4,5} acidic or basic reaction conditions are unavoidable. Thus, general conditions to handle acid- or base-sensitive functionalities remain elusive. In fact, most of the 1,5-diketones described previously^{4,5} contain mainly alkyl or aryl substituents.

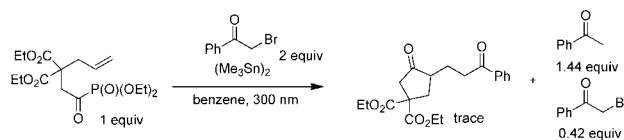
In contrast, radical-based approaches to the synthesis of such 1,5-dicarbonyl compounds have not been as extensively explored as their ionic counterparts. Radical reactions are able to proceed in the absence of strong basic or acidic conditions and should therefore be better suited for

[†] Nanyang Technological University.[‡] Ecole Polytechnique.(1) For reviews on annulation from 1,5-diketones, see: (a) Jung, M. E. *Tetrahedron* **1976**, 32, 3. (b) Gawley, R. E. *Synthesis* **1976**, 777.(2) (a) Pchelintseva, N. V.; Chalaya, S. N.; Kharchenko, V. G. *Zh. Org. Khim.* **1990**, 26, 1904. *Chem. Abstr.* **1991**, 115, 71334. (b) Owton, W. M.; Gallagher, P. T.; Brunavs, M. *Synth. Commun.* **1992**, 22, 351.(3) (a) Rapson, W. S.; Robinson, R. J. *Chem. Soc.* **1935**, 1285. (b) Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, 42, 4777.(4) Selected examples of modification of the enolate: (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, 85, 207. (b) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, 49, 779. (c) Takahashi, A.; Yanai, H.; Taguchi, K. *Chem. Commun.* **2008**, 2385.(5) Selected examples of modifications of the enone: (a) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, 95, 6152. (b) Brewster, J. H. and Eliel, E. L. In *Organic Reactions*; Adams, R., Eds; John Wiley and Sons: New York, 1953; Vol. 7, pp 99–197.

acid- or base-sensitive functionalities. To date, only a handful of radical-mediated 1,5-diketone syntheses have been reported.^{6,7} Some of these earlier studies⁶ involved ketonyl radical addition to specific surrogates of enones and are often accompanied by oxidation and reduction or protection and deprotection steps, which can be tedious and troublesome. Hence, it is still of synthetic significance to develop a facile and direct means to access highly functionalized 1,5-diketones from simple precursors.

We have previously reported tin-mediated intramolecular radical acylation using alkenylacylphosphonate as a carbonyl group acceptor with various radicals to afford functionalized cyclic ketones.⁸ Building on these studies, we reasoned that using ketonyl radicals to accomplish first an intermolecular addition to an alkenylacylphosphonate, followed by intramolecular cyclization with β -elimination of a phosphonate radical from the intermediate alkoxy radical should lead to the target 1,5-diketones.

Scheme 1. Tin-Mediated Reaction of α -Bromo Acetophenone with an ω -Alkenyl Acylphosphonate



Unfortunately, preliminary investigations toward this end proved disappointing. Despite our earlier success with various radical precursors, the ketonyl type radicals could not be made to react efficiently by application of classical methods.⁸ For example, the use of hexamethylditin with α -halo ketones resulted in mostly reduction to the ketone and only a trace amount of the desired product was observed (Scheme 1).

Nevertheless, we decided to seek alternate systems to add a ketonyl radical onto alkenylacylphosphonates. Since keto-xanthates derived from the same α -halo ketones have been shown to act as efficient ketonyl radical precursors for the intermolecular addition to olefins,⁹ we therefore decided to investigate their reactivity with ω -alkenylacylphosphonates in the hope that we might overcome the problems encountered with α -halo ketones.¹⁰

Gratifyingly, the keto-xanthates proved to be effective reaction partners with the ω -alkenylacylphosphonates. The phosphonate radical was found to effectively mediate the xanthate transfer in this radical cascade reaction,

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(10) Our attempts to explore an alternative method under tin-free conditions using α -halo ketones were unsuccessful.

allowing the synthesis of 5- or 6-membered carbocyclic 1,5-diketones from primary keto-xanthates bearing alkyl (**6a**, **7a**), chloro (**6b**, **7b**), and aryl (**6c**, **7c**) substituents in good yields (72–80%). Secondary xanthates bearing alkyl substituents (**6d**, **7d**) reacted reasonably well to give moderate yields of 63 and 61%, respectively (Figure 1).

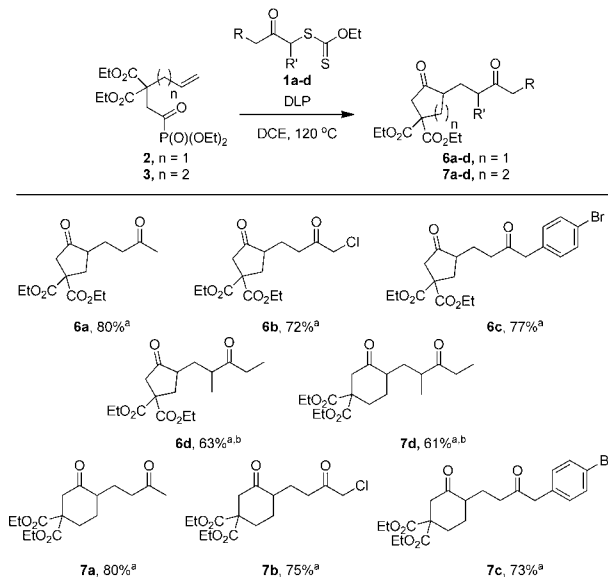
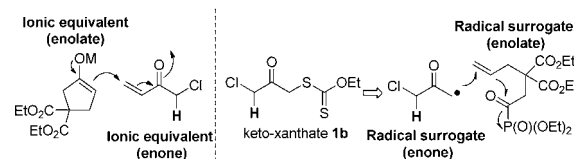


Figure 1. Synthesis of 5- and 6-carbocyclic 1,5-diketones. Conditions: (a) To **1** and **2** or **3** (1.5 equiv) in anhydrous 1,2-dichloroethane (DCE, 0.5 M in the xanthate) heated to reflux under argon was added 0.2 equiv of dilauroyl peroxide (DLP) every hour until **1** was mostly consumed as indicated by TLC; isolated yields were based on **1**. (b) DLP was added at a rate of 0.3 equiv every hour; diastereomers (1:1) were not separated.

It should be noted that keto-xanthates **1a–h** are readily synthesized^{11a} from commercially available materials as opposed to the corresponding enones used in the ionic synthetic pathway to 1,5-diketones (Scheme 2).

Scheme 2. Comparison of Keto-xanthate **1b** as a Radical Surrogate for Its Corresponding Enone Equivalent



Moreover, the presence of particularly acidic hydrogens α to the ketone in some of these structures or a reactive α -chlorine, as in **6b** or **7b**, would also pose problems in an acidic or basic medium, leading to uncontrolled mixtures

(11) Keto-xanthates **1b**, **1e**, and **1f** can be readily synthesized in one step from 1,3-dichloroacetone, ethyl 4-chloroacetoacetate, and ethyl 2-chloroacetoacetate: (a) Greef, M. D.; Zard, S. Z. *Org. Lett.* **2007**, 9, 1773. (b) Tate, E. Z.; Zard, S. Z. *Tetrahedron Lett.* **2002**, 43, 4683.

of side products arising from further cyclization or other transformations.

With these results in hand, we extended the sequence to heteroatom substituted ω -alkenylacylphosphonates to test the applicability of this method to form heterocyclic 1,5-diketones. *O*-Allyl acylphosphonate **4** reacted with various functionalized keto-xanthates **1a–f** to give the corresponding benzopyran 1,5-diketones or 3-substituted chroman-4-ones in moderate to good yields (49–75%, Figure 2). Chroman-4-ones are known to self-polymerize under basic conditions during alkylation reactions,^{12a} the present radical approach therefore offers a comparatively milder synthetic alternative. Yields of benzopyran 1,5-diketones **8a–d** were slightly lower but comparable to those of the carbocyclic 1,5-diketones **6** and **7**. Keto-xanthates **1e** and **1f** showed that the ethyl ester functionality is well-tolerated as well. For secondary keto-xanthate **1f**, the intermediate carbon radical is strongly stabilized by two carbonyl groups and its addition to the olefin becomes therefore less effective, leading to lower yield (49%). It is worth emphasizing again that vinyl ketones containing an α -chlorine or α -ester group corresponding to keto-xanthates **1b**, **1e**, and

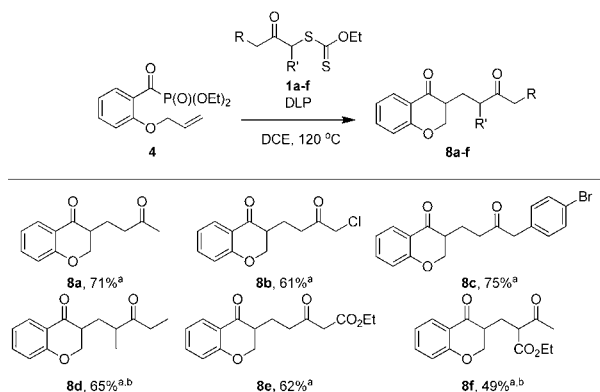


Figure 2. Synthesis of benzopyran 1,5-diketones. Conditions: (a) To **1** and **4** (1.5 equiv) in anhydrous 1,2-dichloroethane (DCE, 0.5 M in the xanthate) under argon was added 0.2 equiv of dilauroyl peroxide (DLP) every hour until **1** was mostly consumed as indicated by TLC; isolated yields were based on **1**. (b) DLP was added at 0.3 equiv every hour; diastereomers (1:1) were not separated.

1f would pose severe difficulties in both preparation^{13,14} and utilization as enone counterparts in ionic conjugate addition.

As expected, the *N*-hetero alkenylacylphosphonates **5** reacted cleanly with functionalized keto-xanthates **1a–h**,

proving the ability to construct nitrogen-containing heterocycles as well. Tetrahydroquinoline 1,5-diketones **9a–e,g,h** were thus obtained in good yields (Figure 3, 61–83%) with the exception of **9f**. The excessive stability of the intermediate carbon radical, as discussed above, had a deleterious effect on the yield (**9f**, 40%). The ready formation of compounds **9g** and **9h** further demonstrates the broad functional group tolerance of this radical process.

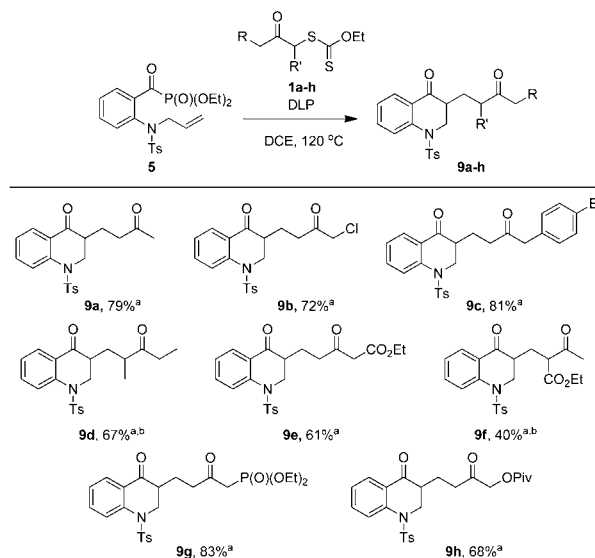


Figure 3. Synthesis of tetrahydroquinoline 1,5-diketones. Conditions: (a) To **1** and **5** (1.5 equiv) in anhydrous 1,2-dichloroethane (DCE) (0.5 M in the xanthate) heated to reflux under argon was added 0.2 equiv of DLP every hour until **1** was mostly consumed as indicated by TLC; isolated yields were based on **1**. (b) DLP was added at 0.3 equiv every hour; diastereomers (1:1) were not separated.

As mentioned previously, 1,5-diketones pave an easy route to functionalized pyridines. Selected examples of pyridine synthesis are shown in Figure 4. Treatment of the functionalized 1,5-diketones with excess ammonium acetate in refluxing acetic acid led to either functionalized carbocyclic (**10** and **11**) or heterocyclic (**12–15**) fused-ring pyridines, including a tetrasubstituted pyridine **14** in good yields (76–85%, Figure 4). Pyridine **15** can be further transformed by the Horner–Wadsworth–Emmons reaction to give vinylpyridine derivatives.¹⁵ Fused-ring pyridines such as **10–15** are an important class of aromatic nitrogen heterocycles; they exhibit high bioactivity and are valuable for medicinal purposes.^{16,18} The present method offers yet another alternative to access novel

(12) (a) Padfield, E. M.; Tomlinson, M. L. *J. Chem. Soc.* **1950**, 2272. A five-step synthesis to a similar benzopyran 1,5-diketone has been reported; (b) Venkateswararao, E.; Sharma, V. K.; Lee, K.-C.; Roh, E.; Kim, Y.; Jung, S.-H. *Bioorg. Med. Chem.* **2013**, *21*, 2544.

(13) Preparation of the vinyl ketone equivalent of keto-xanthate **1e** proceeds in only 43% yield over two steps: Ghosh, S.; Rivas, F.; Fischer, D.; Gonzalez, M. A.; Theodorakis, E. A. *Org. Lett.* **2004**, *6*, 941.

(14) The preparation of the vinyl ketone equivalent of keto-xanthate **1f** proceeds in a low yield of 22%: Cocker, W.; McMurry, T. B. H. *J. Chem. Soc.* **1955**, 4430.

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(16) Rizk, T.; Bilodeau, E. J.-F.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8325.

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variations of structurally similar multisubstituted fused-ring pyridines^{16–18} and thus improves the diversity needed for structure–activity relationship (SAR) studies.

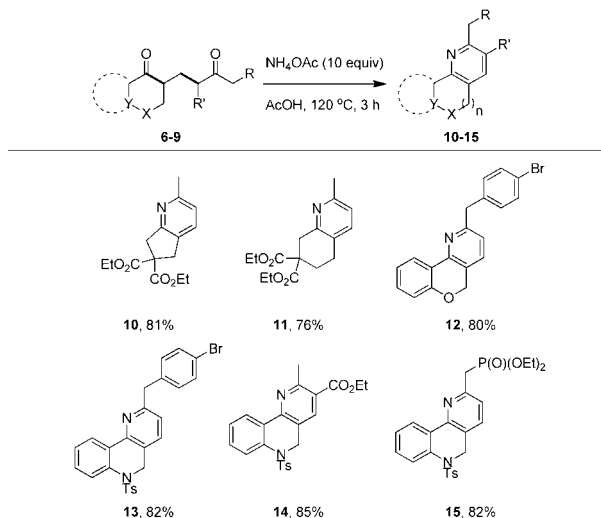


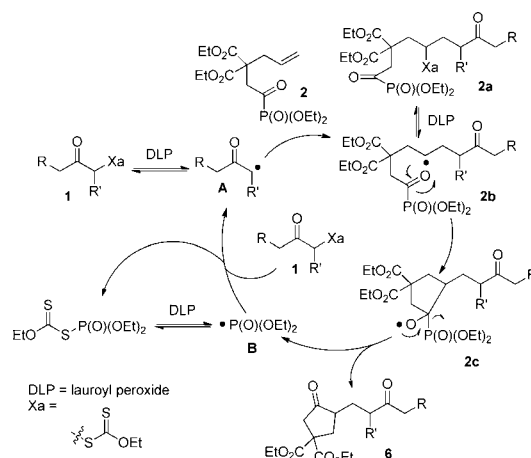
Figure 4. Synthesis of functionalized fused-ring pyridines.

In the proposed mechanistic pathway (Scheme 3), keto-xanthate **1** is converted into ketonyl radical **A** through initiation by dilauroyl peroxide (DLP) and undergoes radical addition to the alkenylacylphosphonate **2**, followed by a xanthate transfer to give the xanthate adduct **2a**. This xanthate **2a** is further reversibly converted into radical intermediate **2b** by more DLP and subsequently undergoes a 5-*exo-trig* cyclization to give alkoxy radical **2c**. β -Fragmentation of **2c** then leads to the 1,5-diketone **6** with the extrusion of phosphonate radical **B**, which could then participate in another xanthate exchange with keto-xanthate **1** and reintroduce the ketonyl radical **A**, thus propagating the radical chain process. The key to success lies in the degenerate nature of the xanthate exchange, which provides the intermediate radicals with an extended lifetime, even in a concentrated medium. With α -halo ketones, it is possible that formation of a tin or boron enolate in the case of $(\text{Me}_3\text{Sn})_2$ or Et_3B -initiation causes premature reduction of ketonyl radical **A**.¹⁹ Currently, this is only observed for the ketonyl radicals, while other type of radicals⁸ have been reported to work efficiently with alkenylacylphosphonates.

(18) Cailly, T.; Begtrup, M. *Tetrahedron* **2010**, *66*, 1299.

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Scheme 3. Proposed Radical Cycle for Phosphonate Radical-Mediated Xanthate Transfer



In conclusion, we have demonstrated an effective combination play of alkenylacylphosphonates and keto-xanthates, leading to a direct and facile access to functionalized 1,5-diketones without the need for further transformation. This is an example showing the use of keto-xanthates as successful alternatives in place of α -halo ketones, where the radical halogen atom transfer process is mostly ineffective. α -Iodo ketones are generally unstable and the fast iodine transfer cannot be exploited in this instance. The strategic use of alkenylacylphosphonate grants flexibility to construct carbocycles or heterocycles in the 1,5-diketones via the radical cascade reaction while the keto-xanthate partner allows easy incorporation of a great variety of functionalities. Moreover, some of the keto-xanthates can be prepared from commercially available substrates easier and faster than the usual ionic precursors required for the synthesis of 1,5-diketones. In addition, these 1,5-diketones can be further elaborated into novel fused-ring pyridines.

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

The authors declare no competing financial interest.