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Room Temperature Acylketene Formation? 1,3-Dioxin-4-ones via Silver(I) Activation of Phenylthioacetoacetate in the Presence of Ketones

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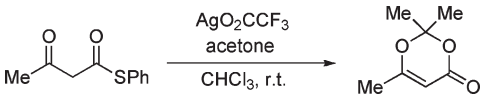
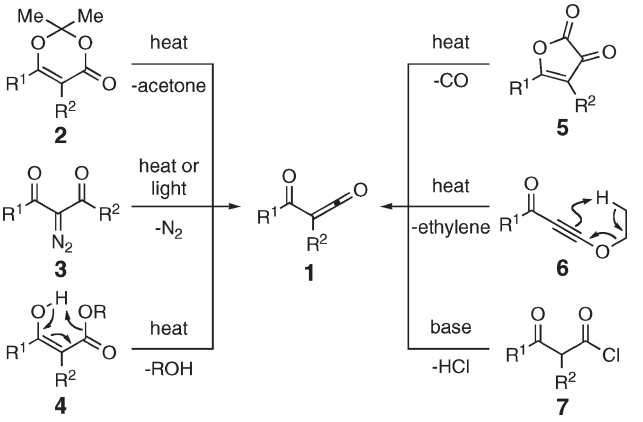


Silver(I) activation of thioacetoacetates in the presence of ketones produces 1,3-dioxin-4-ones. Mechanistic studies addressing the intermediacy of an acylketene intermediate are described.

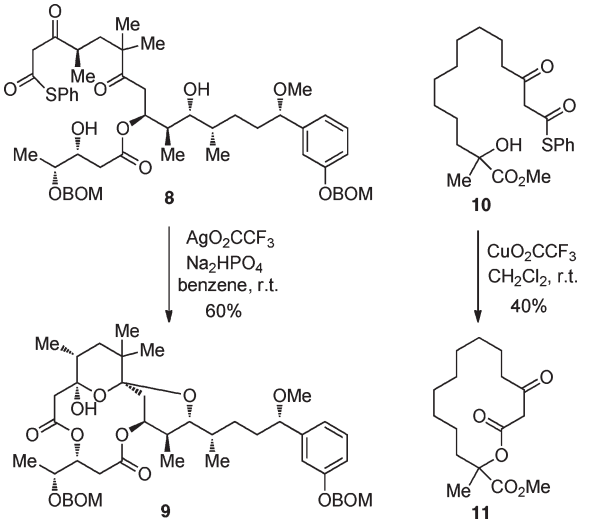
Acylketenes **1** are interesting, highly reactive, and useful intermediates from the perspectives of both mechanism and complex molecule synthesis.[1] The parent acetylketene (**1**, R^1 = Me, R^2 = H) has a half-life of <1 μs in water.[2] In most instances, the fate of acylketenes **1** is to acylate nucleophilic oxygen or nitrogen functional groups to produce esters/acids or amides. Many of the known methods for the generation of acylketenes involve elevated temperatures (Scheme 1), which is limiting in some instances.[3] Thermolysis of 1,3-dioxin-4-ones **2** is the most common and convenient method for forming the parent acetylketene.[4] Thermolysis or photolysis of 2-diazo-1,3-dicarbonyl species **3** leads to carbene formation and insertion into a neighboring carbonyl.[5] Thermolysis of β-ketoesters **4** leads to the loss of ROH via concerted elimination.[6] Furan 2,3-diones **5** chelotropically extrude carbon monoxide when heated.[7] Acylated ethoxy alkynes **6** undergo a retro-ene reaction to eliminate ethylene.[4] Finally, β-ketoacid chlorides such as **7** are susceptible to elimination of HCl.[8]

From some related acylative reactions, the intermediacy of acylketenes has not been clearly demonstrated or, perhaps,

SCHEME 1. Methods of Acylketene Formation



SCHEME 2. Activation of Thioacetoacetates as Reported by Kishi (8 → 9) and Ley (10 → 11) and Co-workers



considered. Ester/lactone formation from β-ketothioesters falls in this category. Reports from the Kishi[9] and Ley[10] laboratories demonstrate that macrolactonizations can be effectively achieved using a thiophilic metal to activate the β-ketothioester moiety present in the cyclization precursor (cf. **8** → **9** and **10** → **11**, Scheme 2). We became intrigued by the possibility that these reactions might involve the intermediacy of acylketenes, analogous to those described in our earlier report on dual macrolactonization/pyran hemiketal formation from a dioxinone precursor.[11]

The intermediacy of acylketenes was not invoked to account for the lactonizations shown in Scheme 2, in part because silver(I) and copper(I) salts were known to also

(1) For a review on application of acylketene intermediates to natural product synthesis, see: Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022–3034.
(2) Chiang, Y.; Guo, H. X.; Kresge, A. J.; Tee, O. S. *J. Am. Chem. Soc.* **1996**, *118*, 3386–3391.
(3) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219–1248.
(4) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105–5108.
(5) Horner, L.; Spietschka, E. *Chem. Ber.* **1952**, *85*, 225–229.
(6) Freiermuth, B.; Wentrup, C. *J. Org. Chem.* **1991**, *56*, 2286–2289.
(7) Kol'tsova, S. V.; Feshin, V. P. *Russ. J. Org. Chem.* **2001**, *37*, 1616–1620.
(8) Bell, K.; Sadasivam, D. V.; Gudipati, I. R.; Ji, H.; Birney, D. *Tetrahedron Lett.* **2009**, *50*, 1295–1297.
(9) Park, P. U.; Broka, C. A.; Johnson, B. F.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 6205–6207.
(10) Booth, P. M.; Fox, C. M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 121–129.
(11) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9743–9746.

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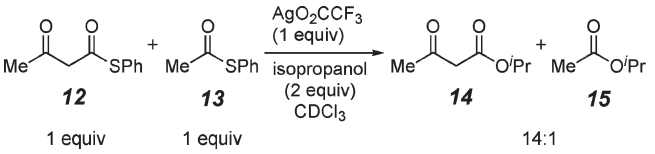
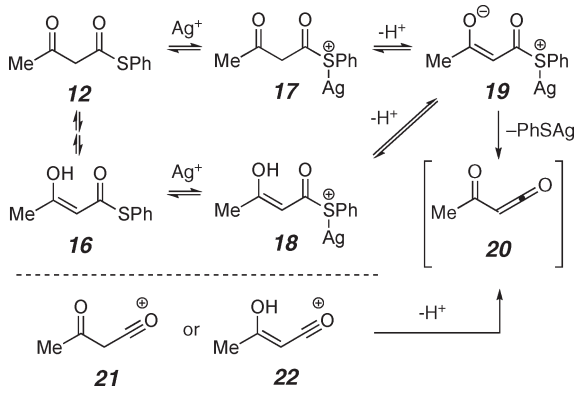
SCHEME 3. Competitive Activation of Thioesters



SCHEME 4. Silver Activation of Phenyl Thioacetoacetate

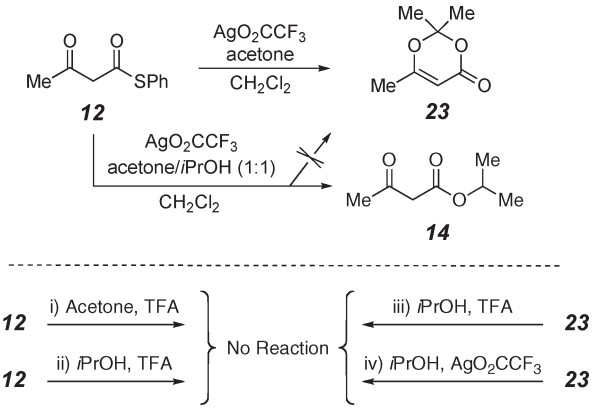


activate simple thioesters lacking β-keto groups.[12] However, we conjectured that there might be significant differences in the rates of activation of thioesters having a β-keto group versus those that do not. We first tested this hypothesis by exposing a 1:1 mixture of phenyl thioacetoacetate (**12**) and phenyl thioacetate (**13**) to isopropyl alcohol with AgO_2CCF_3 in $CDCl_3$ and found that **12** was preferentially consumed, giving a 14:1 ratio of isopropyl acetoacetate (**14**) and isopropyl acetate (**15**) (at ~80% conversion, Scheme 3 and Supporting Information).[13]

This preferential reaction of **12** led us to the mechanistic considerations presented in Scheme 4. Silver(I) ion could complex to the thioacetoacetate **12** or its enol **16**. Either of the resulting cationic intermediates **17** and **18**, upon proton loss, would give the zwitterion **19**, which could collapse directly to acetylketene (**20**) [Douglas and co-workers have shown[14] that E1cb elimination from the anion of thioacetoacetates (acetoacetyl CoA) is facile]. While acylium ions **21** and **22** (from **17** or **18**, respectively) cannot be ruled out as intermediates, such a pathway seems unlikely given the observed lower reactivity of phenyl thioacetate (**13**).

Since acetylketene (**20**) is known to be trapped by ketones to form 1,3-dioxin-4-ones (cf. **2**), we reasoned it might be possible to trap the intermediate ketene if thioacetoacetate activations are proceeding via these reactive species. Additionally, acylketenes are known to be trapped faster (ca. 3 orders of magnitude) by alcohols [to generate β-ketoesters (**4**)] than by ketones [to generate dioxinones (**2**)]. Therefore,

SCHEME 5. Dioxinone Formation and Control Experiments



we would not expect dioxinones to be formed in the presence of alcohols.[15] In testing this hypothesis, we observed that the addition of silver trifluoroacetate to phenyl thioacetoacetate (**12**) in the presence of acetone in $CDCl_3$ at room temperature resulted in formation of dioxinone **23** (Scheme 5, top).[16] Additionally, when isopropyl alcohol was present in the reaction medium (*i*PrOH/acetone ~1:1), none of **23** was observed; instead, isopropyl acetoacetate (**14**) was formed. Both of these results are consistent with the intermediacy of acetylketene (**20**).[17]

Control experiments were run to establish that silver(I) is playing a definitive role in the activation process (Scheme 5, bottom): (i) Formation of dioxinone **23** in the absence of AgO_2CCF_3 is not acid-catalyzed because phenyl thioacetoacetate (**12**) is unreactive when treated with acetone and TFA. (ii) Esterification to produce **14** is also not acid-catalyzed because **12** is unreactive in the presence of *i*PrOH and TFA.[18] Dioxinone **23** is stable when treated with (iii) *i*PrOH/TFA or (iv) *i*PrOH/AgO_2CCF_3. Taken collectively, these results show both that silver is necessary and that the observed selectivity for reaction with alcohols over ketones is kinetic in nature. In other words, dioxinone **23** is not an intermediate en route to **14**.

We probed some of the generality of this new dioxinone forming reaction between these acylketenes and various ketones. Results are shown in Scheme 6. Good yields were obtained for products **25a**−**c**; more hindered ketones [$(iPr)_2CO$ or Bn_2CO] gave only trace amounts of the corresponding dioxinone. This is likely because the starting acetoacetate derivative itself contains a relatively unhindered ketone that will compete with more hindered ketone partners in trapping the acylketene intermediate. For this reason, we used a 3:1 ratio of **24** to **12** to obtain the indicated yields.[19] Substitution

(12) For comparisons of mercury, silver, and copper salts for the activation of thioesters, see: Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758.

(13) For the synthesis of **12** (by refluxing 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one with thiophenol) see: Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431–2435.

(14) (a) Douglas, K. T.; Yaggi, N. F. *J. Chem. Soc., Chem. Commun.* **1980**, *15*, 728–730. (b) Douglas, K. T.; Alborz, M.; Rullo, G. R.; Yaggi, N. F. *J. Chem. Soc., Chem. Commun.* **1982**, 245–246.

(15) Competitive trapping of acetylketene with a 20-fold excess of cyclohexanone vs pentanol leads to a ~300:1 ratio of alcohol trapping over ketone trapping. See: Birney, D. M.; Xu, X. L.; Ham, S.; Huang, X. M. *J. Org. Chem.* **1997**, *62*, 7114–7120.

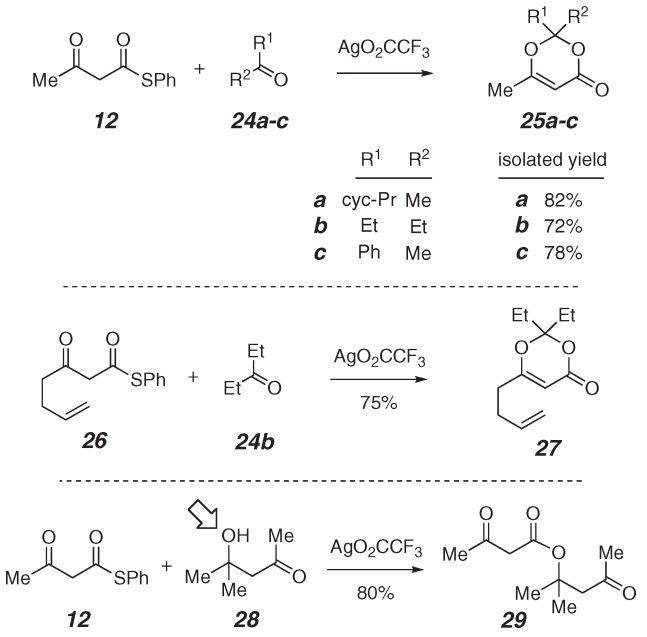
(16) While we cannot rule out the intermediacy of a mixed anhydride like $MeCOCH_2CO_2COCF_3$ in these reactions, it is noteworthy that use of silver phosphate or silver triflate was also found to effect this transformation.

(17) We did not observe any species attributable to acetylketene when monitoring reaction progress by ^1H NMR spectroscopy. This was not unexpected given that (i) the only stable acylketenes are those bearing two sterically demanding groups (e.g., **1**, $R^1 = R^2 = {}^t$Bu), which lock the species into the less reactive *s-trans* conformation (Leung-Toung, R.; Wentrup, C. *J. Org. Chem.* **1992**, *57*, 4850−4858), and (ii) acetylketene dimerizes and oligomerizes upon being warmed from −77 K by itself and reacts with alcohol traps between −90 and −50 °C.[6]

(18) Fischer esterification to form $iPrO_2CCF_3$ was observed instead.

(19) Experiments in which hindered ketones or no ketone (or alcohol) at all were used gave rise to detectable (^1H NMR spectroscopy) amounts of the acetylketene homodimer, dehydroacetic acid (3-acetyl-2-hydroxy-6-methyl-4*H*-pyran-4-one), along with other byproducts.

SCHEME 6. Dioxinone Formation from Silver Activation of Thiophenyl Acetoacetate



on the thioacetoacetate was also tolerated; the allyl-containing thioacetoacetate derivative **26** was successfully converted to dioxinone **27** in 75% yield. Finally, an internal competition experiment was performed using diacetone alcohol (**28**) as the trapping agent. The tertiary alcohol was preferentially trapped to give **29** in 80% isolated yield (no dioxinone formation was observed). This selectivity ($k_{alcohol} > k_{ketone}$) is also consistent with the intermediacy of an acetylketene (**20**).

In conclusion, the transformation of phenyl thioacetoacetate to 1,3-dioxin-4-ones can be accomplished by activation with AgO_2CCF_3 in the presence of ketones. This represents a simple method for the synthesis of 1,3-dioxin-4-ones. Mechanistic studies, including the preferential trapping by alcohols over ketones, point to the intermediacy of acylketenes. As such, silver activation of β-ketothioesters represents a mild and convenient set of conditions for the generation of these reactive intermediates.

Experimental Section

General Experimental Procedure for Dioxinone Formation. Synthesis of 25b. In a 6 dram screw-capped vial, thioester **12** (0.112 g, 0.577 mmol), 3-pentanone (**24b**, 0.153 g, 1.78 mmol), and $CDCl_3$ (2.0 mL) were added. Silver trifluoroacetoacetate (0.140 g, 0.639 mmol) was added to the stirred reaction mixture. After 1.5 h, the suspension was filtered through silica gel using ethyl acetate as the eluent. After concentration in vacuo, the residue was purified by flash chromatography (20% EtOAc/hex) to give **25b** (70.1 mg, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (q, J = 1.0 Hz, 1H), 1.99 (d, J = 1.0 Hz, 3H), 1.98 (dq, J = 15.0, 7.5 Hz, 2H), 1.96 (dq, J = 15.0, 7.5 Hz, 2H), and 0.98 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 162.0, 110.8, 93.7, 28.2, 20.1, and 7.6; HRMS (ESI) calcd for ($C_9H_{14}O_3$ + Na^+) 193.0835, found 193.0853; IR (neat) 2979, 2945, 2886, 1736, 1722, 1642, 1459, 1393, 1348, 1313, 1320, 1209, 1185, 1161, 1060, 1053, 998, 952, 905, and 806 cm^{-1}; TLC R_f = 0.45 in 20% EtOAc/hexanes.

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Supporting Information Available: Experimental procedures and ^{1}H NMR, ^{13}C NMR, HRMS, and IR spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.