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Highly Efficient Methyl Ketone Synthesis by Water-Assisted C−C Coupling between Olefins and Photoactivated Acetone

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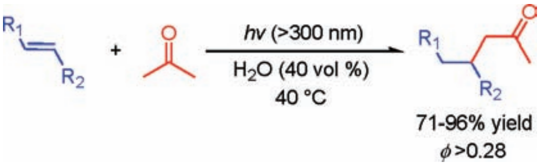
ABSTRACT



Photoirradiation of an acetone/water mixture containing olefins affords the corresponding methyl ketones highly efficiently via a water-assisted C—C coupling between acetonyl radical and olefins.

Ketones occupy pivotal positions as intermediates as well as final products in the synthesis of natural products and pharmaceutical materials. Traditional alcohol oxidation requires stoichiometric amounts of inorganic oxidants, notably chromium reagents, with concomitant formation of copious heavy-metal waste.[1] Recent advances in oxidation catalysts allow clean alcohol oxidation with molecular oxygen; [2] however, these processes require noble metal catalysts. Another powerful method for ketone synthesis is the olefin oxidation (Wacker reaction)[3] and the cross-coupling reaction between organoborons and haloarenes or acyl halides (Suzuki−Miyaura reaction); [4] however, both methods require Pd-based catalysts.

It is well-known that photoexcited acetone undergoes Norrish type I,[5] sensitization,[6] and hydrogen abstraction reactions.[7] With olefins, the photoexcited acetone undergoes [2 + 2]cycloaddition to produce oxetane.[8] A few reports reveal that addition of acetone to olefin proceeds via acetonyl radical formation; [9] photoirradiation of acetone containing

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(1) (a) Cainelli, G.; Cardillo, G. *Chromium Oxidants in Organic Chemistry*; Springer: Berlin, 1984. (b) Ley, S. V.; Madin, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 251.

(2) (a) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636–1639. (b) Graves, C. R.; Zeng, B.-S.; Nguyen, S. T. *J. Am. Chem. Soc.* **2006**, *128*, 12596–12597. (c) Schultz, M. J.; Park, C. C.; Sigman, M. S. *Chem. Commun.* **2002**, 3034–3035.

(3) (a) Cornell, C. N.; Sigman, M. S *Inorg. Chem.* **2007**, *46*, 1903–1909. (b) Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2796–2797. (c) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481–485. (d) ten Brink, G.-J.; Arends, I. W. C. E.; Papadogianakis, G.; Sheldon, R. A. *Chem. Commun.* **1998**, 2359–2360.

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(8) (a) Büchi, G.; Inman, C. G.; Lipinsky, E. S. *J. Am. Chem. Soc.* **1954**, *76*, 4327–4331. (b) Turro, N. J.; Dalton, J. C.; Dawes, K.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Shore, N. *Acc. Chem. Res.* **1972**, *5*, 92–101. (c) Small, R. D., Jr.; Scaiano, J. C. *Chem. Phys. Lett.* **1978**, *59*, 246–248.

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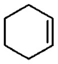
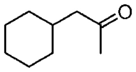
cyclic or exocyclic olefins, such as norbornene and methylenecycloalkanes, affords the corresponding acetone−olefin adducts (methyl ketones). This photochemical C−C coupling reaction proceeds at ambient temperature with acetone, which is cheap, clean, and safe and, hence, has a potential as a new methyl ketone production process; however, the reaction suffers from low selectivity and low yield.

Here, we present highly efficient and selective methyl ketone production, achieved by photoirradiation of an acetone/water mixture containing olefins (see the Table of Contents graphic). This extremely simple photoprocess, efficiently promoted just by water addition, is driven by hydration of acetone-derived radicals, which leads to an enhancement of methyl ketone formation and a suppression of byproduct formation.

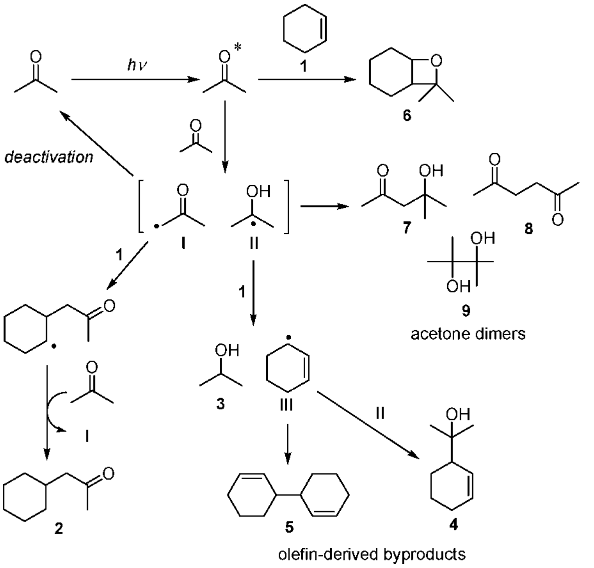
The efficacy of adding water to acetone is evident from the reaction with cyclohexene (**1**) as a substrate. Table 1 shows the yield of 1-cyclohexylpropan-2-one (**2**) obtained by photoirradiation at >300 nm.[10] In pure acetone (entry 1), the yield of **2** is only 15%. In contrast, addition of 40 vol % water (entry 2) leads to drastic yield enhancement for **2** (43%). A similar enhancement (38%) is observed with D_2O (entry 3), but other solvents are ineffective (entries 4−7).

Table 1. Results of Photoreaction of Cyclohexene (**1**) in Acetone Solutions Containing Various Cosolvents (40 vol %)[a]

entry	cosolvent	substrate	product	yield / %[b]
1		 **1**	 **2**	15
2	H_2O			43
3	D_2O			38
4	CH_3OH			7
5	CH_3CN			7
6	benzene			0
7	*n*-hexane			9

[a] Reaction conditions: acetone solution (10 mL), **1** (0.2 mmol), λ >300 nm (Xe lamp), photoirradiation time (6 h), temperature (40 °C).[10] [b] Determined by GC.

Scheme 1. Reaction of Photoactivated Acetone in the Presence of Cyclohexene (**1**)



As described,[8,9,11–13] reaction of photoexcited acetone in the presence of **1** proceeds via the following mechanism (Scheme 1): the excited-state acetone undergoes [2 + 2]cycloaddition to **1** to form **6** (oxetane).[8] The excited-state acetone also undergoes hydrogen abstraction from ground-state acetone to produce acetonyl (**I**) and 2-hydroxy-2-propyl (**II**) radical pairs.[11] These radical pairs undergo fast recombination (deactivation to ground-state acetones) or dimerization (formation of **7**−**9**).[11,12] The methyl ketone (**2**) is formed by a radical addition of **I** to alkene **1** followed by hydrogen abstraction from ground-state acetone.[9] In contrast, radical **II** abstracts an allylic hydrogen of **1** to produce 2-propanol (**3**) and cyclohexenyl radical (**III**). The radical **III** reacts with radical **II** or itself and produces cyclohexene-derived byproducts (**4** and **5**).[13]

The water-induced enhancement of the methyl ketone (**2**) formation is probably due to the suppression of the radical pair recombination (**I** and **II**) by hydration of each radical. Figure 1 (black bar) shows the effect of water amount on the product distribution of **1**. Formation of **2**, **3**, and **6** is enhanced with an increase in the water amount up to 40%. The increased **6** formation is due to the stabilization of intermediate by high polarity of water.[8c] Compounds **2** and **3** form via the reaction of **1** with respective radicals **I** and **II**. These radical pairs are rapidly deactivated by recombination.[12] The enhanced formation of **2** and **3** indicates that water addition suppresses the radical pair recombination. It is well-known that, in aqueous solution, carbonyl[14] and hydroxyl[15] compounds are hydrated via a hydrogen-bonding interaction. The suppression of the radical pair recombination is probably due to the hydration of each radical. As shown in Figure 1, the amount of acetone dimers (**7**−**9**) decreases

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(9) (a) Reusch, W *J. Org. Chem.* **1962**, *27*, 1882–1883. (b) Majerski, K. M.; Pavlović, D.; Kulyk, M. Š *J. Org. Chem.* **1993**, *58*, 252–254. (c) Chung, W.-S.; Ho, C.-C. *Chem. Commun.* **1997**, 317–318.

(10) Photoreaction procedures are as follows: each olefin was dissolved in an acetone solution (10 mL) within a Pyrex glass tube (i.d. 10 mm; capacity, 20 cm^3), where the solvents were used without purification. The tube was sealed using a rubber septum cap and purged with nitrogen. The tube was photoirradiated with magnetic stirring by a Xe lamp (2 kW; Ushio Inc; light intensity, 32.1 mW m^{-2} at 300−340 nm) or a high-pressure Hg lamp (300 W; Eikohsha Co. Ltd.; light intensity, 38.2 mW m^{-2} at 300−340 nm). Substrate and product concentrations were determined by GC−FID (Shimadzu GC-1700), where the product identifications were made by GC−MS (Shimadzu GCMS-QP 5050A). The detailes are described in: (a) Shiraishi, Y.; Saito, N.; Hirai, T. *J. Am. Chem. Soc.* **2005**, *127*, 8304–8306. (b) Shiraishi, Y.; Saito, N.; Hirai, T. *J. Am. Chem. Soc.* **2005**, *127*, 12820–12822.

(11) Nakashima, M.; Hayon, E *J. Phys. Chem.* **1971**, *75*, 1910–1914.

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(15) (a) Filder, J.; Rodger, P. M. *J. Phys. Chem. B* **1999**, *103*, 7695–7703. (b) Ruckenstein, E.; Shulgin, I. L.; Tilson, J. L. *J. Phys. Chem. A* **2005**, *109*, 807–815.

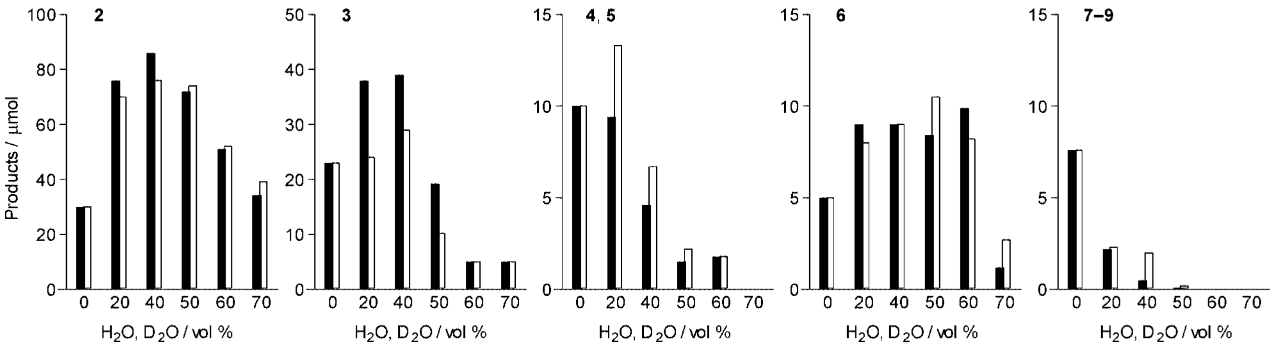

Figure 1. Product distribution of **1** during photoirradiation (λ >300 nm, Xe lamp) of (black) acetone/water and (white) acetone/D_2O mixture as a function of H_2O or D_2O amount. Reaction conditions are the same as those in Table 1.[10]

with an increase in the water amount. This indicates that recombination of the radical pairs is in fact suppressed by water addition. This enhances the addition of radical **I** to **1**, resulting in methyl ketone (**2**) formation enhancement.

The water addition selectively enhances the methyl ketone formation (addition of radical **I** to **1**) while maintaining the activity of radical **II** low. As shown in Figure 1 (black bar), without water, yields of **2** and **3** are similar. Upon addition of 40 vol % water, **2** yield increases by 3-fold, while **3** yield increases only by 1.5-fold. This suggests that water addition selectively enhances the activity of radical **I**, although both radicals are hydrated. The activity difference between radicals **I** and **II** is probably due to the different hydration degree. As reported,[16] strong hydration takes place around the highly polarized molecules. The radical **II** contains a highly polarized hydroxyl group and, hence, is hydrated more strongly than the radical **I**. The strong hydration probably makes the radical **II** less reactive, resulting in low **3** yield enhancement. This assumption is supported by experiments with D_2O in place of water (Figure 1, white bar). The **2** yield increases with D_2O addition, as is also the case with water, whereas the **3** yield enhancement with D_2O is much lower. D_2O solvates the solutes more strongly than water because of stronger hydrogen-bonding interaction.[14a] The lower **3** yield enhancement with D_2O is therefore probably because the strong hydration of the radical **II** suppresses the reaction with **1**. In contrast, weakly hydrated radical **I** may react efficiently with **1**, thus resulting in high **2** yield enhancement. The above findings suggest that the selective methyl ketone formation, simply driven by water addition, is probably due to the "selective" hydration toward the respective acetone-derived radicals, **I** and **II**.

Another notable feature of the present methyl ketone production process is the high performance at ambient temperature. Figure 2 shows the temperature-dependent change in the product distribution of **1** during reaction with 40% water. The **6** formation is suppressed with a rise in temperature due to rapid deactivation of the excited-state acetone.[8b] In contrast, **2** yield increases with a rise in temperature. The hydrogen-bonding interaction is strengthened at higher temperature.[14a] This probably suppresses the recombination of the radicals **I** and **II** more, resulting in **2** yield enhancement. At higher temperature, formation of **3**, **4**, **5**, and **7**−**9** byproducts is much suppressed. This may be because the strengthened hydration makes the radical **II** less reactive. The above findings reveal that the present photoprocess shows the best performance at 40 °C; this allows simple photoreaction control without severe conditions.

The proposed photoprocess with 40% water is tolerant of other olefins. As summarized in Table 2, several olefins are successfully converted to the corresponding methyl ketones with very high yields (>70%). The quantum yields of the methyl ketone formation are determined to be >0.28,[17] indicating that the photoprocess proceeds highly efficiently. It must also be noted that the photoprocess is applicable for production of long-chain methyl ketones, which are difficult to achieve by other conventional processes;[3c,d] for example, 1-dodecene and 1-icosene are successfully converted to the corresponding methyl ketones with 93 and 71% yields, respectively (entries 12 and 15). In addition, the 0.1 mol L^{-1} scale reaction is also successful (entries 3, 6, 13, and 18), even though in these cases the reaction proceeds heterogeneously due to low solubility of olefins and products.

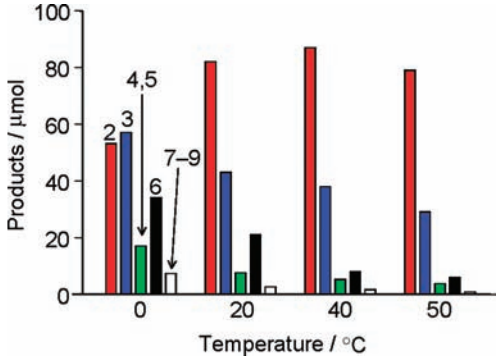

Figure 2. Temperature-dependent change in product distribution of **1** during photoirradiation (λ >300 nm, Hg lamp) of an acetone solution containing 40 vol % water. Reaction conditions are the same as those in Table 1.[10]

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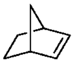
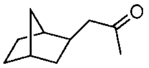
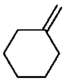
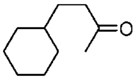
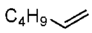
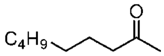
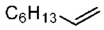
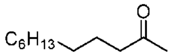
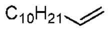
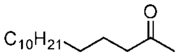
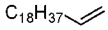
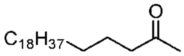
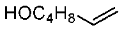
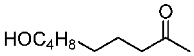
(16) (a) Kamlet, M. J.; Abboud, J.-L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877–2887. (b) Reichardt, C. *Solvents and Solvents Effects in Organic Chemistry*, 3rd ed; Wiley-VCH: Weinheim, 2003; p 432.

Table 2. Methyl Ketone Formation from Various Olefins with Photoactivated Acetone [a]

entry	water / vol %	olefin	concentration / mM	t / h	conversion / %	product	yield / %[b]	Φ[c]
1	0		20	6	100		71	0.20
2	40		20	6	100		90(88^e)	0.28
3	40		100^d	24	99		94	
4	0		20	6	73		43	0.12
5	40		20	6	99		92(80^e)	0.29
6	40		100^d	36	99		78	
7	0		20	12	89		63	
8	40		20		100		85	
9	0		20	6	37		21	0.06
10	40		20	6	99		89(86^e)	0.28
11	0		5	6	63		35	
12	40		5	6	100		93(82^e)	
13	40		100^d	72	96		73	
14	0		5	12	68		50	
15	40		5		75		71	
16	0		20	6	55		27	0.07
17	40		20	6	100		96(92^e)	0.30
18	40		100^d	24	99		78	

[a] Reactions were carried out with Xe lamp (λ > 300 nm).[10] [b] Yields were determined by GC analysis; values in parentheses are the yields of the isolated products. [c] Quantum yield of the methyl ketone formation determined by photoreaction experiments with a 313 nm emission line (Hg lamp; filtered through a potassium chromate solution (K_2CrO_4, 0.27 g L^{-1}; K_2CO_3, 1 g L^{-1}); light intensity, 3.1 mW m^{-2}). [d] Reaction proceeds heterogeneously because olefins and products are not fully dissolved in solution. [e] ^{1}H NMR charts of the respective isolated products are shown in the Supporting Information (Figures S1−S5) to show the purity of the products.

In conclusion, we found that simple photoreaction system with an acetone/water mixture allows highly efficient and selective methyl ketone production. Methyl ketone formation via the acetonyl radical addition to olefins also proceeds thermochemically;[18] however, these methods require metal oxidants for the radical formation. Our photoprocess exhibits significant advantages: (i) metal-free, (ii) cheap reactant (acetone), (iii) cheap additive (water), and (iv) mild reaction conditions (40 °C). Although the detailed mechanism remains to be clarified, applying the basic concept presented here may help realize methyl ketone synthesis in an economically and environmentally friendly way.

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Supporting Information Available: Materials, general procedure, and ^{1}H NMR charts for the isolated products in Table 2 (Figures S1−S5). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Quantum yields were determined with a *trans*-stilbene actinometer (Φ = 0.45, in benzene): Lewis, F. D.; Johnson, D. E. *J. Photochem.* **1977**, *7*, 421–423.

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