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Iodine-mediated *Z*-selective oxidation of ketones to α,β-unsaturated esters: synthesis and mechanistic studies

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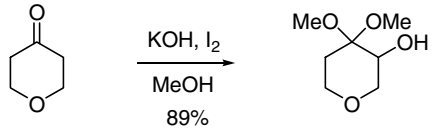
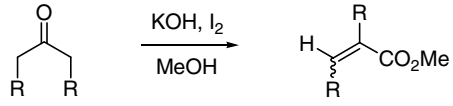
Abstract—The *Z*-selective oxidation of simple acyclic ketones to *Z*-2,3-trisubstituted α,β-unsaturated esters is described. Enolates generated under the reaction conditions undergo double iodination followed by a Favorskii-related rearrangement to the unsaturated ester. This reaction represents the first stereoselective one-step transformation of ketones to α,β-unsaturated esters. Mechanistic studies suggest that an electrocyclic reaction governs the Favorskii-related rearrangement.

The conversion of dihaloketones to α,β-unsaturated esters has received considerable attention and serves as a valuable alternative to the use of Horner–Wadsworth–Emmons phosphonoacetate reagents.[1] The Favorskii-related rearrangement of 1,1-dihalo[2] and 1,3-dihalo[3] ketones to α,β-unsaturated esters has been reported, including stereospecific reactions that afford the *cis*-α,β-unsaturated ester.[3a–e] This reaction has been applied primarily to the synthesis of 3-disubstituted acrylates, including the known stereospecific examples,[3a–e] while there are few reports of its use for the synthesis of 2,3-trisubstituted acrylates[2c,d] and no selective examples. One drawback is that these protocols typically involve a separate step to prepare and isolate the dihaloketone.[4] Furthermore, despite the numerous reports, little experimental evidence has been disclosed to either support or refute the various mechanistic proposals that have been offered to explain this transformation. A stereoselective synthesis of *Z*-2,3-trisubstituted acrylates would be valuable since these homologues of angelic acid esters have been studied as medicinal leads[5] as well as food flavorants and fragrance compounds.[6] A one-step procedure which bypasses the isolation of the dihaloketones would also be an improvement over the existing stereoselective protocols. In this letter, we report the one-step synthesis of *Z*-2,3-trisubstituted α,β-unsaturated esters from saturated ketones that proceeds via a diiodoketone intermediate. We disclose our detailed mechanistic studies as well and proposed a mechanism for this interesting reaction.

In the course of our investigations of the iodine-mediated oxidation of carbonyls, we observed a marked difference in reactivity between cyclic versus acyclic ketones. Subjection of cyclic six-membered ring ketones to 1 equiv of iodine and 2 equiv of KOH in MeOH afforded α-hydroxyketals (Eq. 1).[7] On the other hand, when acyclic ketones were subjected to the identical conditions at room temperature α,β-unsaturated esters were the only identifiable products (*Z*:*E* = 3:2) (Eq. 2).



(1)



(2)

A similar one-step procedure using iodine generated under electrochemical conditions has been reported,[2c,d] albeit without selectivity for either olefin isomer. In addition to improved practicality versus the use of electrochemical cells, the use of elemental iodine allowed for the opportunity to manipulate reaction conditions in order to achieve selectivity. Among the numerous variables examined, we found that order of addition was crucial for obtaining high selectivity. Addition of KOH/MeOH solution to a cold solution of ketone and

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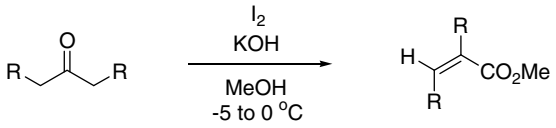
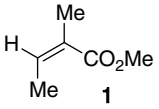
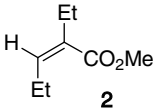
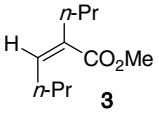
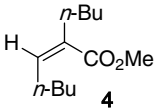
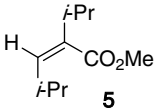
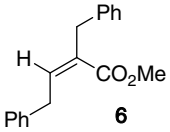
I_2 in MeOH allowed for the stereoselective preparation of *Z*-acrylates. By contrast, the reverse order of addition resulted in lower selectivity (*Z*:*E* = 7:1). The optimized conditions involved the slow addition of KOH (4.8 equiv) in MeOH to a −5 °C MeOH solution containing ketone and I_2 (2.2 equiv). This procedure was applied to a series of simple symmetric ketones and the results are presented in Table 1.[8]

Unbranched symmetric ketones are excellent substrates for the oxidation reaction. Branching at the β-position of the ketone leads to a lower *Z*:*E* ratio (Table 1, entry 5), as does conducting the reaction at room temperature (*Z*:*E* = 11:1 in the case of 3-pentanone). While water is present in the reaction mixture (KOH serves as a convenient precursor to KOMe), saponification of the product esters was not observed under these reaction conditions.

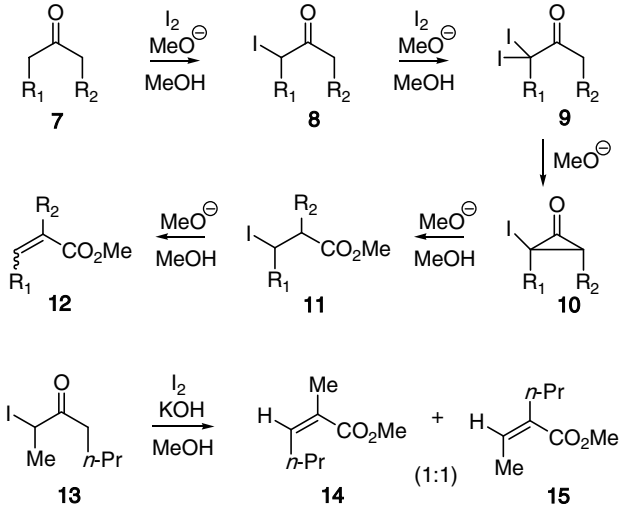
We also considered extending this reaction to unsymmetrical ketones. Previous electrochemical studies,[2c,d] however, demonstrated a lack of regioselectivity with respect to the products formed when unsymmetrical ketones (**7**, $R_1 \neq R_2$) are employed. The lack of selectivity seemingly follows from the previously proposed mechanism,[2c,d] whereby α-iodoketone **8** undergoes further iodination to α,α-diiodoketone **9**. A presumed Favorskii rearrangement via α-iodocyclopropanone **10** to the saturated β-iodoester **11** is followed by elimination of HI to afford **12**. Accordingly, a selective initial enolization (selective production of **8**, where $R_1 \neq R_2$) would result in selective product formation. With this in mind, we subjected the known iodoketone **13**[9] to modified reaction conditions. Treatment of **13** with 1.1 equiv of I_2 and 3.4 equiv of KOH in MeOH afforded a 1:1 mixture of regioisomeric acrylates **14** and **15** (*Z*:*E* = 25:1).

Table 1. Synthesis of α,β-unsaturated esters from ketones



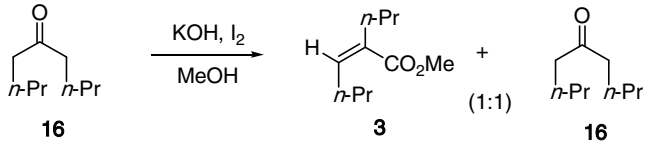
Entry	R	Product	*Z*:*E*[a]	Yield[b] (%)
1	Me	 **1**	20:1[c]	60[d]
2	Et	 **2**	25:1	72
3	*n*-Pr	 **3**	25:1	80
4	*n*-Bu	 **4**	25:1	83
5	*i*-Pr	 **5**	9:1	75
6	CH_2Ph	 **6**	20:1	75

[a] Ratio determined by ^1H NMR.
[b] Isolated yield.
[c] Ratio determined by HPLC.
[d] LC assay yield.



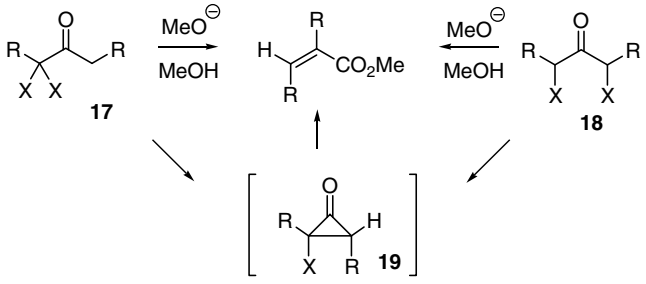
The conversion of **13** to **14** and **15** effectively ruled out the possibility of selective product formation from unsymmetrical ketones. Furthermore, this experiment suggested that a different mechanism may be operating and would explain the observed product distribution. Though the synthetic utility of the reaction is relegated to the synthesis of angelate homologues, we became intrigued by the mechanism of the overall transformation and turned our attention towards detailed mechanistic studies. We also hoped to shed light on the various mechanistic proposals in the literature for the conversion of dihaloketones to α,β-unsaturated esters.

We began by verifying the importance of a diiodoketone (**9** or an isomer) as an intermediate under our reaction conditions. Subjection of 5-nonanone (**16**) to only half of the reagents (2.4 equiv KOH, 1.1 equiv of I_2) under otherwise identical reaction conditions led to the formation of a 1:1 mixture of **3** and unreacted **16**. By analogy to the haloform reaction, this suggested that an initially

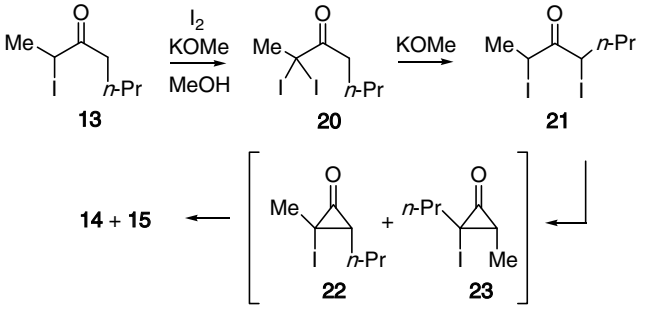


formed α-iodoketone underwent enolization and iodination faster than the starting ketone.

Since both α,α-dihaloketones **17**[2] and α,α′-dihaloketones **18**[3] are reported to undergo alkoxide-promoted conversion to α,β-unsaturated esters via an intermediate α-halocyclopropanone (**19**), we sought to distinguish between the two possible intermediates in the present study. Due to their symmetry, the substrates examined in Table 1 could not provide information to differentiate these two pathways. Thus the reactivity of iodoketone **13** was probed further.

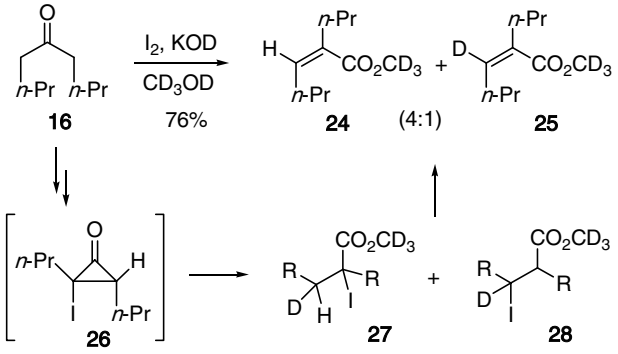


Compound **13** was treated with 0.8 equiv of I_2 and 0.7 equiv of KOH in MeOH in an NMR experiment. The newly observed chemical shifts were consistent with the formation of α,α-diiodoketone **20**.[10] Further treatment with 1.0 equiv of KOH led to the formation of small amounts of acrylates **14** and **15**, along with a new compound whose NMR data was consistent with α,α′-diiodoketone **21**.[11] Based on this result, we propose that an α,α′-diiodoketone (**21**) is the actual diiodoketone species which undergoes Favorskii-type rearrangement to the product α,β-unsaturated esters. In the case of unsymmetrical ketones, two intermediate iodocyclopropanones **22** and **23** can form, which likely accounts for the unselective formation of both **14** and **15**.

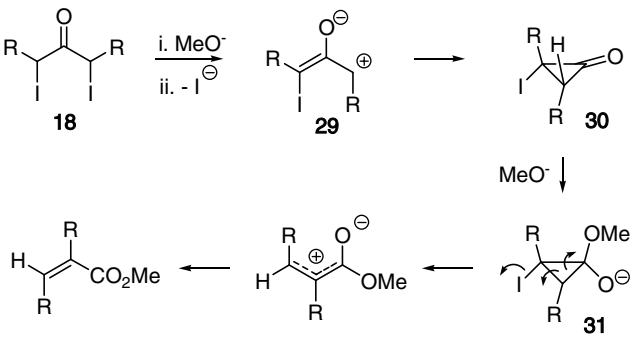


We next turned our attention towards elucidating the conversion of iodocyclopropanone to α,β-unsaturated ester. Two mechanisms have been proposed in the literature. The first involves a classical Favorskii rearrangement (i.e., **10** → **11** → **12**),[2,3h] while the second involves an electrocyclic reaction.[3a,b,12]

The present transformation likely does not follow from the classical Favorskii mechanism. We base this conclusion on the results from a deuterium labelling experiment, where subjection of 5-nonanone (**16**) to the reaction conditions (KOD, I_2, CD_3OD) afforded the acrylate products **24** and **25** with only 20% D incorporation (80% H) at the β-position. If operative, the classical Favorskii pathway would have afforded both saturated iodo-esters **27** and **28**, followed by elimination of HI.[13] If **27** were formed exclusively, then the product would have 100% D incorporation at the β-position of the product acrylate. If **28** were formed exclusively, then the amount of D incorporation at the β-position of the product would depend upon the kinetic isotope effect, but should be >50% since normal primary kinetic isotope effect are observed in E2 elimination reactions. The observation of only 20% D incorporation in the product suggested that neither **27** nor **28** were precursors to the product acrylate.



Since saturated iodo-esters (e.g., **27** and **28**) were not likely intermediates, it seemed plausible that the iodocyclopropanone was converted directly to the ester product. A proposed mechanism that accounts for this is an electrocyclic reaction. The transformation of halocyclopropanone intermediates into α,β-unsaturated carbonyls has been explained by the disrotatory electrocyclic ring opening of halocyclopropane to the allyl cation.[3a,b,14a] In this scenario, enolization of the intermediate **18** would lead to the presumed *cis*-cyclopropanone **30**,[12,14a] perhaps via disrotatory electro-cyclic ring closure of zwitterion **29**.[15] Though we have not been able to observe the cyclopropanone intermediate, the stereochemistry of the observed acrylate product implies the cis configuration according to the Woodward–Hoffmann rules.[12] Additionally, Conia's verification of these rules in the stereoselective conversion of analogous *cis*-chlorocyclopropanols to *Z*-enals lends support to this



speculated stereochemistry.[14a] Addition of methoxide to **30** would afford **31**, which can undergo alkoxide-promoted disrotatory electrocyclic ring opening with concerted expulsion of iodide[3a,b,12] to afford the *Z*-acrylate. Given the available data, this seems to be the most reasonable mechanism.

In summary, we have described the iodine-mediated one-step oxidation of symmetric ketones to *Z*-α,β-unsaturated esters. This method offers rapid access to valuable acrylates from easily accessible and inexpensive starting materials, with no organic waste products. Mechanistic studies suggest that an α,α′-diiodoketone undergoes Favorskii-related rearrangement, via an electrocyclic reaction, to afford α,β-unsaturated ester.

References and notes

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7. Zacuto, M. J.; Cai, D. *Tetrahedron Lett.* **2005**, *46*, 447.
8. General experimental procedure for the synthesis of **1**–**5**: Ketone (5.0 mmol) was added to a solution of I_2 (2.8 g, 11 mmol) in MeOH (20 mL), then cooled to −5 °C. A solution of KOH (1.6 g of A.C.S. 85% KOH assay pellets) in MeOH (18 mL) was then added over 25 min. The solution was then allowed to warm gradually to room temperature, and then stirred for an additional 1 h. The solution was then concentrated, and the resulting slurry was diluted with Pentane and filtered. Concentration afforded the crude α,β-unsaturated ester which was suitable for further use, but could be purified by silica gel chromatography. Data for **1**: ^{1}H NMR, ^{13}C NMR, MS and HPLC agree with data obtained from commercially available material. Data for **2**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.83 (t, $J = 7.6$ Hz, 1H), 3.73 (s, 3H), 2.45–2.35 (m, 2H), 2.26 (q, $J = 7.6$ Hz, 2H), 1.02 (t, $J = 7.6$ Hz, 3H), 1.00 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 168.6, 142.2, 132.8, 51.0, 27.4, 22.9, 13.9, 13.6. Data for **3**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.84 (t, $J = 7.2$ Hz, 1H), 3.73 (s, 3H), 2.37 (td, $J_1 = 7.6$ Hz, $J_2 = 7.6$ Hz, 2H), 2.22 (t, $J = 7.6$ Hz, 2H), 1.48–1.37 (m, 4H), 0.92 (t, $J = 7.2$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 168.7, 141.6, 131.8, 50.9, 36.5, 31.5, 22.6, 22.1, 13.6, 13.4. Data for **4**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.84 (t, $J = 7.4$ Hz, 1H), 3.73 (s, 3H), 2.39 (td, $J_1 = 7.2$ Hz, $J_2 = 7.2$ Hz, 2H), 2.23 (t, $J = 7.6$ Hz, 2H), 1.43–1.25 (m, 8H), 0.99 (t, $J = 7.2$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 168.8, 141.7, 132.0, 51.1, 34.3, 31.7, 31.3, 29.3, 22.4, 22.2, 13.9, 13.9. Data for **5**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (dd, $J_1 = 9.6$ Hz, $J_2 = 1.2$ Hz, 1H), 3.74 (s, 3H), 2.88–2.78 (m, 1H), 2.69–2.57 (m, 1H), 1.04 (t, $J = 6.8$ Hz, 3H), 0.98 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 169.5, 141.8, 136.6, 50.9, 31.2, 28.5, 22.7, 21.7. Data for **6**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.20 (m, 10H), 6.11 (t, $J = 7.6$ Hz, 1H), 3.85 (d, $J = 7.6$ Hz, 2H), 3.72 (s, 3H), 3.63(s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 167.8, 141.6, 140.0, 139.2, 131.6, 128.7, 128.5, 128.5, 128.3, 126.2, 126.2, 51.3, 40.4, 35.8.
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11. The ^{1}H and ^{13}C data agrees well with known data for 2,4-diiodo-3-pentanone: see Montaña, A. M.; Grima, P. M. *Synth. Commun.* **2003**, *33*, 265–279; For a similar isomerization, see: Rappe, C. *Acta Chem. Scand.* **1963**, *17*, 2140.
12. (a) Hoffmann, R.; Woodward, R. B. *Accounts Chem. Res.* **1968**, *1*, 17, and references cited therein; (b) DePuy, C. H. *Accounts Chem. Res.* **1968**, *1*, 33.
13. The iodocyclopropanone intermediate **26** is presumed to contain a proton at the α-carbon, as isotopic scrambling at the α-carbon of the ketone should be minimal since the procedure involves the slow addition of base to a mixture of the ketone and I_2. This assumption was affirmed when the reaction was run to 50% conversion and NMR data indicated only 20% D incorporation into the unreacted ketone.
14. For related studies on isolated cyclopropane systems, see: (a) Conia, J.-M.; Blanco, L. *New J. Chem.* **1983**, *7*, 399; (b) Slougui, N.; Rousseau, G. *Synth. Commun.* **1982**, *12*, 401; (c) Slougui, N.; Rousseau, G. *Tetrahedron* **1985**, *41*, 2643.
15. For a review of the mechanism of the Favorskii rearrangement, see: (a) Baretta, A.; Waegell, B. In *Reactive Intermediates*; Abramovich, R. A., Ed.; Plenum: New York, 1982; Vol. 2, Chapter 6. The stereochemistry of **29** is speculated, but implied by the presumed stereochemistry of **30** according to the Woodward–Hoffmann rules (see, Refs. 12, 14a).