PTSA-Catalyzed Reaction of Alkyl/Aryl Methyl Ketones with Aliphatic Alcohols in the Presence of Selenium Dioxide: A Protocol for the Generation of an \(\alpha\)-Ketoacetals Library

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Supporting Information

ABSTRACT: A novel approach has been developed for the synthesis of a wide range of \(\alpha\)-ketoacetals by the reaction of alkyl/aryl methyl ketones and aliphatic alcohols in the presence of selenium dioxide catalyzed by \(p\)-toluenesulfonic acid. This method represents a general route to obtain a wide variety of \(\alpha\)-ketoacetals in a simple, rapid, and practical manner. This approach is particularly attractive because of the easy availability of the starting materials, mild reaction temperature, and good yields of the products. The resulting \(\alpha\)-ketoacetals are of much synthetic value as organic intermediates.

INTRODUCTION

The \(\alpha\)-ketoacetals are important functional moieties and are useful building blocks in organic synthesis. They are useful intermediates in that they provide an array of functional groups that are extremely valuable in organic syntheses. For instance the \(\alpha\)-ketoacetals are a key intermediate in the synthesis of various biological active compounds such as chiral \(\alpha\)-hydroxy acetals, chiral \(\alpha\)-amino acetals, chiral auxiliaries, and cyanosilylation and also for the construction of important heterocycles. Several methods have been described for the preparation of \(\alpha\)-ketoacetals. Goswami et al., reported the synthesis of aliphatic \(\alpha\)-ketoacetals starting from ketones via a two step procedure using \(\text{SeO}_2\). Tiecco and co-workers reported the synthesis of \(\alpha\)-ketoacetals catalyzed by diphenyl diselenide and an excess of ammonium peroxydisulfate under reflux conditions (Scheme 1a). Ayala-Mata and group employed Weinreb amides as a starting material for the synthesis of \(\alpha\)-ketoacetals (Scheme 1b). More recently, we have reported the synthesis of phenylglyoxal diethylacetals via the reaction of aromatic ketones with triethylorthoformate in the presence of \(\text{H}_2\text{SeO}_3\) catalyzed by \(\text{BF}_3\cdot\text{Et}_2\text{O}\) (Scheme 1c). This method, though simple is limited by the use of triethylorthoformate as the sole source of alkoxide nucleophile. Generally, most of the other reported methods involved multistep reactions. Besides, the high cost of the reagents coupled with sensitive reaction conditions limit their scope of applications. Development of an alternative method for the synthesis of \(\alpha\)-ketoacetals with wide substrate scope starting from simple and easily available starting materials would therefore be a welcome addition to synthetic organic chemists.

The reactive behavior of \(\text{SeO}_2\) toward organic substrates in the presence of a Lewis acid or a strong organic acid, however, has found few or no mention at all in the literature. Earlier we

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Scheme 1. Synthesis of \(\alpha\)-Ketoacetals

Previous Work

(a) \[ \text{PhMe}_2\text{BH} \xrightarrow{\text{SyO}^2-}\cdot\text{MeO} \text{Me} \]

(b) \[ \begin{align*} \text{CH}_2\text{CHO} \xrightarrow{\text{NH}_4\text{S}_2\text{O}_8, \text{THF}, 70^\circ\text{C}} & \quad \text{R} \\text{CH}_2\text{CO} \text{Me} \\text{O} \text{Me} \\ \text{R} & \quad \text{CH}_2\text{CHO} \end{align*} \]

(c) \[ \begin{align*} \text{CH}_2\text{CHO} \xrightarrow{\text{H}_2\text{SeO}_3, \text{BF}_3\cdot\text{Et}_2\text{O}, \text{THF}} & \quad \text{R} \\text{CH}_2\text{CO} \text{Me} \\text{O} \text{Me} \\ \text{R} & \quad \text{CH}_2\text{CHO} \end{align*} \]

Our Work

\[ \begin{align*} \text{R} \xrightarrow{\cdot\text{OH}} & \quad \text{R} \text{CH}_2\text{CO} \text{Me} \\text{O} \text{Me} \\ \text{R} & \quad \text{CH}_2\text{CHO} \end{align*} \]

\[ \begin{align*} \text{R} \xrightarrow{\text{SeO}_2, \text{PTSA}, \text{40-60}^\circ\text{C}, 5-12 \text{ h}} & \quad \text{R} \text{CH}_2\text{CO} \text{Me} \\text{O} \text{Me} \\ \text{R} & \quad \text{CH}_2\text{CHO} \end{align*} \]

from simple and easily available starting materials would therefore be a welcome addition to synthetic organic chemists.
reported an efficient regio-selective protocol for the C–C bond formation by an unexpected α, α-diarloration of aromatic ketones in the presence of selenium dioxide, catalyzed by boron trifluoride etherate. This unusual reactivity of SeO2 toward aromatic ketones in the presence of a Lewis acid prompted us to explore its reactions with organic substrates by varying the nature of the acid and the solvent used. Since then, we have further demonstrated this unique reactivity of SeO2 with aromatic ketones by changing the acid catalyst and/or the solvent used, leading to the formation of important organic intermediates.

As part of our on-going investigation on the synthetic utility of selenium dioxide, we wish to report here an efficient general method for the synthesis of α-ketoacetals from a wide range of ketones and alcohols in presence of SeO2 catalyzed by p-toluenesulfonic acid (PTSA) (Scheme 1).

![Scheme 1](https://example.com/scheme1)

**RESULTS AND DISCUSSION**

Initially, when a mixture of 1-(3-nitrophenyl)ethanone (1h) (1.0 mmol), ethanol (2a) (1 mL), SeO2 (0.5 equiv), and PTSA (0.5 equiv) was stirred at room temperature for 12 h, only a trace amount of the product was formed as observed by thin-layer chromatography (TLC) (Table 1, entry 1). When the reaction temperature was raised to 60 °C for 8 h, the yield increased to 52% (Table 1, entry 2). Any further increase in the temperature did not increase the yield any further. Further optimization reactions by varying the number of equivalents of selenium dioxide and PTSA (Table 1, entry 2–6) were carried out. It was found that (0.7 equiv) of SeO2 and (1.0 equiv) of PTSA gave optimum yield of the product (85%) (Table 1, entry 4). To establish whether PTSA is unique to this reaction, other organic acids such as TFA and CH3COOH were employed and in both cases the desired product was not formed. It may be noted that the use of either SeO2 or PTSA alone failed to give the desired product.

With the optimized conditions in hand, the scope and generality of the reaction of aryl methyl ketones with alcohols were investigated. First, the reaction demonstrated a wide substrate scope in terms of the aromatic ketone (1) with ethanol (2a) (Scheme 2). Aryl methyl ketones bearing electron-neutral (4-H), electron-donating [e.g., 4-Me, 4-OH, 4-OME, and 3,4-(OMe)2] or electron-withdrawing (e.g., 3-NO2 and 4-NO2) substituent in the ring were successfully converted to the corresponding products 3a−d, 3e−i, and 3g−i in moderate-to-good yields (59−90%). The procedure was also found to be compatible with halogenated aryl methyl ketone (4-Br, 4-Cl), which gave the desired products in good yields (3c, 71%; 3d, 74%). The scope of the reaction was also extended to sterically hindered 2-acetyl naphthalene (1j), which readily yielded product 3j in 78% yield.

Second, homologs of alcohol from the aliphatic series (Scheme 2) were randomly selected. Both primary and secondary aliphatic alcohols easily undergo double nucleophilic attack on the α-carbon atom of the ketone to give the desired products 3k−w in moderate-to-good yields (60−89%). Methanol (2b), 1-propanol (2c), 1-butanol (2d), 1-hexanol (2e), benzyl alcohol (2f), and iso-butanol (2g) readily reacted with aryl methyl ketones bearing electron-withdrawing group (3-NO2), electron-donating groups [3,4-(OMe)2], and halogenated aryl methyl ketones (4-Br, 4-Cl) to give the corresponding products 3k−p and 3s−t in moderate-to-good yields (60−88%). Ordinarily one would have expected that long-chain aliphatic alcohol would not react because of steric consideration. Surprisingly however, the reaction with cetyl alcohol (2h) proceeded cleanly in 8h to give excellent yields of the desired product (3v, 85%; 3w, 89%). Similarly, secondary alcohols such as iso-propanol (2i) and cyclohexanol (2j) also reacted smoothly to give the corresponding products 3q−r and 3u in satisfactory yields (62−79%). However, tertiary aliphatic alcohol (2k) failed to react evidently because of the bulky nature of the substituent adjacent to the reacting nucleophile 3x.

The methodology was further extended to the reaction of hetero-aryl methyl ketones (4) with aliphatic alcohol (2) which effortlessly gave the desired products 5a−d in moderate-to-good yields (72−93%) (Scheme 3).

To further explore the efficacy of the method, reactions of substituted benzylidene acetones (6) with alcohols (2) were performed (Scheme 4). Benzylidene acetone bearing electron neutral (4-H), electron donating (e.g., 4-Me and 4-OMe), electron withdrawing (4-NO2), or halogenated group (4-Br) all gave the expected products 7a−e in good yield (82−92%).

Having met with unprecedented success in the above reactions, we finally turned to the aliphatic ketones 8. We were delighted to note that the method continues to hold good with representative examples of cyclic and acyclic aliphatic ketones (Scheme 5). Reactions with aliphatic ketones such as acetone (8a), ethyl methyl ketone (8b), and pentanone (8c) proceeded as expected to give the corresponding products 9a−d in moderate yield (62−70%). Reactions with branched aliphatic ketones such as iso-butyl methyl ketone (8d) and isopentyl methyl ketone (8e) also gave the desired products (9e, 69%; 9f, 67%) in good yields. Similarly, secondary aliphatic ketones 3-methyl-2-butanone (8f) and the strained cyclopropyl ketone (8g) afforded the desired products 9g and 9h in 65 and 73% yields respectively.

Previously, we had proposed the reactions to proceed via the intermediate 10 (Scheme 6) where precipitation of elemental selenium occurred. In the present work, particularly, the precipitation of elemental selenium was clean with no formation of colloidal Se. Although we have not succeeded in isolating the intermediate 10 so far, evidently the mechanism follows the same route as reported in our previous work (Scheme 6).

![Scheme 6](https://example.com/scheme6)

**CONCLUSION**

We have developed a simple and efficient approach for the synthesis of α-ketoacetals from aryl/alkyl methyl ketones with...
aliphatic alcohols in the presence of selenium dioxide and PTSA. The methodology further demonstrates its generality for a diversity-oriented synthesis of novel α-ketoacetals library.

Scheme 2. Scope of Aryl Methyl Ketones That Couple with Alcohols

```
R \text{SeO}_2 (0.7 \text{ eq}) \text{ PTSA (1.0 \text{ eq})} \rightarrow R' \text{O} \text{N} \text{R}'
```

| 1 | 2 | 3 |
|---|---|---|
| 3a, 65% (8h) | 3b, 60% (10h) | 3c, 71% (8h) |
| 3d, 74% (8h) | 3e, 50% (10h) | 3f, 90% (8h) |
| 3g, 63% (12h) | 3h, 85% (8h) | 3i, 59% (12h) |
| 3j, 78% (8h) | 3k, 82% (8h) | 3l, 67% (8h) |
| 3m, 86% (12h) | 3n, 75% (9h) | 3o, 88% (8h) |
| 3p, 73% (9h) | 3q, 79% (8h) | 3r, 62% (10h) |
| 3s, 82% (8h) | 3t, 77% (8h) | 3u, 67% (8h) |
| 3v, 85% (8h) | 3w, 89% (8h) | 3x, 0% |

"Reaction conditions: ketones (1) (1.0 mmol), alcohols (2) (1 mL), SeO\textsubscript{2} (0.7 equiv), PTSA (1.0 equiv) at 60 °C, 8−12 h.

Scheme 3. Scope of Heteroaryl Methyl Ketones That Couple with Alcohols

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X = O, S
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\[
\begin{array}{c}
\text{R} \text{SeO}_2 (0.7 \text{ eq}) \text{ PTSA (1.0 \text{ eq})} \rightarrow \text{R'} \text{O} \text{N} \text{R'}
\end{array}
\]

| 4 | 2 | 5 |
|---|---|---|
| 4a, 93% (8h) | 5a, 89% (8h) | 5c, 72% (8h) |
| 4b, 93% (8h) | 5b, 89% (8h) | 5d, 78% (8h) |

"Reaction conditions: ketones (4) (1.0 mmol), alcohol (2) (1 mL), SeO\textsubscript{2} (0.7 equiv), PTSA (1.0 equiv) at 60 °C, 8 h.

Scheme 4. Scope of α, β-Unsaturated Ketones That Couple with Alcohols

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R \text{SeO}_2 (0.7 \text{ eq}) \text{ PTSA (1.0 \text{ eq})} \rightarrow R' \text{O} \text{N} \text{R}'
```

| 6 | 2 | 7 |
|---|---|---|
| 6a, 86% (8h) | 7a, 92% (8h) |
| 6b, 89% (8h) | 7b, 82% (8h) |
| 6c, 89% (8h) | 7c, 85% (8h) |
| 6d, 89% (8h) | 7d, 89% (8h) |

"Reaction conditions: ketones (6) (1.0 mmol), alcohols (2) (1 mL), SeO\textsubscript{2} (0.7 equiv), PTSA (1.0 equiv) at 60 °C, 6−8 h."
Scheme 5. Scope of Aliphatic Ketones That Couple with Alcohols

**Reaction conditions:** ketones (8) (1.0 mmol), alcohol (2) (1 mL), SeO₂ (0.7 equiv), PTSA (1.0 equiv), 40 °C, 5–8 h.

Scheme 6. Plausible Mechanism

The reactions exhibited wide substrate tolerance in both the reactants. The easy availability of the reactants used coupled with the simplicity of the reaction procedure involved will certainly make this methodology a more attractive and viable alternative.

**EXPERIMENTAL SECTION**

**General Methods.** All reagents were purchased from Sigma-Aldrich, TCI Chemicals, and Alfa Aesar and were used without further purification unless noted. Melting points were recorded by the open capillary tube method and are uncorrected. IR spectra were recorded on a PerkinElmer Spectrum 400 FTIR instrument. ¹H NMR and ¹³C [¹H] NMR spectra were recorded on a Bruker Avance II-400 spectrometer in CDCl₃ with TMS as the internal standard. Mass spectral data were obtained with a Waters UPLC-TQD mass spectrometer (ESI-MS). Elemental analyses were carried out on an Elementar Vario EL III CHNS-O analyzer.

**General Procedure for the Synthesis of Compounds 3, 5, 7, and 9.** A mixture of the aromatic ketone 1 or 4 or α, β-unsatuated ketones 6 or aliphatic ketones 8 (1.0 mmol), selenium dioxide (77 mg, 0.7 mmol, 0.7 equiv), PTSA (190 mg, 1.0 mmol, 1.0 equiv), and alcohol 2 (1 mL) was allowed to stir at 40–60 °C for 5–12 h. Then, a thick precipitate of elemental selenium settled at the bottom of the flask which was then filtered off, washed with ethyl acetate (2 × 10 mL), and the combined filtrate was transferred to a separating funnel, washed with conc. sodium bicarbonate solution (2 × 10 mL) followed by brine (2 × 10 mL). The organic layer was separated, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The crude mass was purified by column chromatography using silica gel (100–200 mesh) or flash chromatography using silica gel (230–400 mesh) and ethyl acetate–hexane as the eluent.

**2,2-Diethoxy-1-phenylethanone (3a).** The title compound was prepared via the general procedure from acetophenone 1a (120 mg, 1.0 mmol) and ethanol 2a (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (143 mg, 69% yield); IR (KBr film): 3064, 2979, 2883, 1686, 1599, 1449, 1360, 1266, 1119, 1062 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.17–7.43 (m, 5H), 5.29 (s, 1H), 3.80–3.64 (m, 4H), 1.25 (t, J = 7.2 Hz, 6H) ppm; ¹³C [¹H]NMR (100 MHz, CDCl₃): δ 194.0, 133.7, 133.4, 129.7, 128.3, 102.3, 63.1, 15.2 ppm. MS (ES⁺): for C₁₂H₁₅ClO₃, 242.0; found m/z, 231.8, 131.8, 131.3, 128.6, 103.0, 63.5, 15.1 ppm. MS (ES⁺): for C₁₃H₁₈O₃, 222.1; found m/z, 218.1 [M + Na]⁺.

**1-(4-Bromophenyl)-2,2-diethoxyethanone (3b).** The title compound was prepared via the general procedure from 4-bromo-acetophenone 1c (199 mg, 1.0 mmol) and ethanol 2a (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (143 mg, 69% yield); IR (KBr film): 3030, 2979, 2922, 2870, 1682, 1605, 1574, 1428, 1405, 1358, 1268, 1181, 1122, 1018 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 7.2 Hz, 2H), 5.21 (s, 1H), 3.71–3.56 (m, 4H), 2.34 (s, 3H) ppm; MS (ES⁺): 303.1 [M + Na]⁺.

**2,2-Diethoxy-1-phenylethanone (3c).** The title compound was prepared via the general procedure from 4-methyl-acetophenone 1d (134 mg, 1.0 mmol) and ethanol 2a (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (144 mg, 65% yield); IR (KBr film): 3094, 2979, 2931, 2883, 1693, 1585, 1484, 1400, 1358, 1268, 1181, 1122, 1018 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.99 (d, J = 7.2 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 5.21 (s, 1H), 3.71–3.56 (m, 4H), 2.34 (s, 3H) ppm; MS (ES⁺): 303.1 [M + Na]⁺.
4-hydroxy-acetophenone 1e (136 mg, 1.0 mmol) and ethanol 2a (1 mL). The product was isolated by flash chromatography using 2% ethyl acetate/hexane as an eluent; oil (134 mg, 60% yield); IR (KBr film): 3330, 2982, 2935, 2896, 1675, 1602, 1515, 1443, 1372, 1290, 1164, 1056 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.00 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 6.83 (d, J = 8.4 Hz, 2H), 5.28 (s, 1H), 3.68–3.53 (m, 4H), 1.15 (t, J = 7.2 Hz, 6H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 193.4, 161.8, 132.4, 126.0, 115.5, 101.2, 62.8, 15.1 ppm. MS (ES⁺): for C₆H₄O₂Na₂ 224.1; found m/z, 225.0 [M + H⁺].

2,2-Diethoxy-1-(4-nitrophenyl)ethanone (3f). The title compound was prepared via the general procedure from 4-nitro-acetophenone 1f (165 mg, 1.0 mmol) and ethanol 2a (1 mL). The product was isolated by flash chromatography using 5% ethyl acetate/hexane as an eluent; oil (227 mg, 90% yield); IR (KBr film): 3107, 2975, 2935, 2896, 2844, 1679, 1601, 1575, 1511, 1460, 1422, 1308, 1260, 1173, 1114, 1062, 1029 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.08 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.17 (s, 1H), 3.80 (s, 3H), 3.71–3.55 (m, 4H), 1.17 (t, J = 7.6 Hz, 6H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 192.7, 150.3, 138.0, 131.0, 123.3, 103.7, 64.1, 15.1 ppm. MS (ES⁺): for C₁₄H₁₂O₅ 253.1; found m/z, 276.1 [M + Na⁺].

2,2-Diethoxy-1-(4-methoxyphenyl)ethanone (3g). The title compound was prepared via the general procedure from 4-methoxy-acetophenone 1g (150 mg, 1.0 mmol) and ethanol 2a (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (149 mg, 63% yield); IR (KBr film): 3297, 2975, 2935, 2896, 2844, 1769, 1601, 1575, 1511, 1460, 1422, 1308, 1260, 1173, 1114, 1062, 1029 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.06 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.17 (s, 1H), 3.80 (s, 3H), 3.71–3.55 (m, 4H), 1.17 (t, J = 7.6 Hz, 6H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 192.7, 163.7, 132.1, 130.6, 113.5, 102.5, 63.0, 55.4, 15.2 ppm. MS (ES⁺): for C₁₄H₁₂O₅ 238.1; found m/z, 261.1 [M + Na⁺].

2,2-Diethoxy-1-(3-nitrophenyl)ethanone (3h). The title compound was prepared via the general procedure from 3-nitro-acetophenone 1h (165 mg, 1.0 mmol) and ethanol 2a (1 mL). The product was isolated by flash chromatography using 5% ethyl acetate/hexane as an eluent; oil (215 mg, 85% yield); IR (KBr film): 3088, 2980, 2935, 2885, 1703, 1614, 1558, 1534, 1478, 1441, 1351, 1271, 1228, 1062 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.96 (s, 1H), 8.43 (d, J = 8.8 Hz, 1H), 8.34 (d, J = 6.0 Hz, 1H), 7.58 (t, J = 8.8 Hz, 1H), 5.09 (s, 1H), 3.80–3.57 (m, 4H), 1.09 (s, J = 7.2 Hz, 6H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 192.0, 148.1, 135.6, 134.6, 129.4, 127.5, 125.0, 103.5, 64.1, 15.1 ppm. MS (ES⁺): for C₁₄H₁₂O₅ 253.1; found m/z, 276.1 [M + Na⁺].

2,2-Diethoxy-1-(3,4-dimethoxyphenyl)ethanone (3i). The title compound was prepared via the general procedure from 3,4-dimethoxy-acetophenone 1i (180 mg, 1.0 mmol) and ethanol 2a (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (177 mg, 60% yield); IR (KBr film): 3296, 2939, 2877, 1680, 1595, 1515, 1464, 1421, 1344, 1273, 1228, 1119, 1069, 1024 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.84 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 5.14 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.61–3.43 (m, 4H), 1.61–1.52 (m, 4H), 0.84 (t, J = 7.2 Hz, 6H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 191.7, 152.5, 147.6, 125.7, 123.9, 110.8, 108.9, 102.2, 68.4, 55.0, 54.9, 21.9, 9.5 ppm. MS (ES⁺): for C₁₉H₁₇NO₅ 319.1521; found, 319.1523.

1-(4-Bromophenyl)-2,2-dipropoxyethanone (3n). The title compound was prepared via the general procedure from 4-bromo-acetophenone 1c (199 mg, 1.0 mmol) and 1-propanol 2c (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (220 mg, 70% yield); IR (KBr film): 2965, 2935, 2877, 1690, 1586, 1483, 1396, 1265, 1116, 1071, 1010 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.04 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 9.2 Hz, 2H), 5.13 (s, 1H), 3.69–3.48 (m, 4H), 1.67–1.58 (m, 4H), 0.90 (t,
1.24 (m, 4H), 0.82 (t, 5.03 (s, 1H), 3.73 Hz, 1H), 8.34 (d, 2e (100 MHz, CDCl3):

3-nitro-acetophenone

found C16H23NO5, 309.1; found

125.1, 104.3, 68.5, 31.6, 19.1, 13.7 ppm. MS (ES +): for

C20H31ClO3, 354.2; found

135.6, 125.1, 104.3, 68.1, 31.4, 29.5, 25.6, 22.5, 19.1 ppm. MS (ES +): for

C41H74O3, 614.5; found

1171, 1241, 1013 ppm. MS (ES +): for

C39H62O3N, 472.2; found

377.1859; found, 377.1856.

1,4-Chlorophenyl)-2,2-bis (hexyloxy)ethanone (3p). The title compound was prepared via the general procedure from 4-chloro-acetophenone 1d (154 mg, 1.0 mmol) and hexanol 2e (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (258 mg, 73% yield); IR (KBr film): 3136, 2977, 2934, 2861, 1694, 1589, 1401, 1385, 1284, 1192, 1121, 1092 cm−1; 1H NMR (400 MHz, CDCl3): δ 8.04 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.04 (s, 1H), 3.64–3.44 (m, 4H), 1.56–1.49 (m, 4H), 1.27–1.15 (m, 12H), 0.78 (t, J = 6.8 Hz, 6H) ppm; 13C{1H} NMR (100 MHz, CDCl3): δ 193.1, 139.8, 131.3, 128.5, 103.6, 68.1, 31.4, 29.5, 25.6, 22.5, 19.1 ppm; MS (ES +): for

C20H27BrO3Na, 6040

m/z: [M + Na]+ calcd for C16H19BrO3Na, 275.1259; found, 275.1257.

2,2-Dibutoxy-1-(3-nitrophenyl)ethanone (3o). The title compound was prepared via the general procedure from 3-nitro-acetophenone 1h (165 mg, 1.0 mmol) and 1-butanol 2d (1 mL). The product was isolated by flash chromatography using 5% ethyl acetate/hexane as an eluent; oil (253 mg, 82% yield); IR (KBr film): 3090, 2960, 2875, 1703, 1615, 1580, 1536, 1472, 1438, 1349, 1301, 1266, 1055 cm−1; 1H NMR (400 MHz, CDCl3): δ 9.00 (s, 1H), 8.43 (d, J = 7.2 Hz, 1H), 8.35–8.33 (m, 1H), 7.58 (t, J = 7.2 Hz, 1H), 4.99 (s, 1H), 3.50–3.25 (m, 4H), 1.88–1.78 (m, 2H), 0.83 (t, J = 6 Hz, 12H) ppm; 13C{1H} NMR (100 MHz, CDCl3): δ 192.0, 148.1, 135.6, 134.6, 129.3, 125.2, 104.8, 75.5, 28.5, 19.2, 19.1 ppm. MS (ES +): for

C32H42O5Na, 519.3; found m/z, 327.1 [M + NH4]+. HRMS (ESI) m/z: [M + Na]+ calcd for

C32H42O5Na, 332.3518; found, 332.3514.

1-(4-Chlorophenyl)-2,2-bis (hexyloxy)ethanone (3p). The title compound was prepared via the general procedure from 4-chloro-acetophenone 1d (154 mg, 1.0 mmol) and hexanol 2e (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (258 mg, 73% yield); IR (KBr film): 3136, 2977, 2934, 2861, 1694, 1589, 1401, 1385, 1284, 1192, 1121, 1092 cm−1; 1H NMR (400 MHz, CDCl3): δ 8.04 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.04 (s, 1H), 3.64–3.44 (m, 4H), 1.56–1.49 (m, 4H), 1.27–1.15 (m, 12H), 0.78 (t, J = 6.8 Hz, 6H) ppm; 13C{1H} NMR (100 MHz, CDCl3): δ 193.1, 139.8, 131.3, 128.5, 103.6, 68.1, 31.4, 29.5, 25.6, 22.5, 19.1 ppm; MS (ES +): for

C20H27BrO3Na, 6040

m/z: [M + Na]+ calcd for C16H19BrO3Na, 275.1259; found, 275.1257.
The title compound was prepared via the general procedure from 4-bromobenzaldehyde acetone 6d (225 mg, 1.0 mmol) and iso-amyl alcohol 2i (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (353 mg, 89% yield); IR (KBr film): 2958, 2872, 1700, 1416, 1313, 1165, 1068 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.63 (d, J = 16 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 6.99 (d, J = 16.4 Hz, 1H), 4.68 (s, 1H), 3.67–3.46 (m, 4H), 1.70–1.59 (m, 2H), 1.48–1.43 (m, 4H), 0.84 (d, J = 2 Hz, 6H), 0.82 (d, J = 2.4 Hz, 6H); \(^{13}\)C{\(^1\)H}NMR (100 MHz, CDCl\(_3\)): \(\delta\) 193.0, 142.2, 132.5, 131.1, 128.8, 123.9, 120.2, 101.9, 65.1, 37.3, 23.9, 21.5 ppm. HRMS (ESI) \(m/z\): [M + Na\(^+\)] calcd for C\(_{20}\)H\(_{30}\)BrO\(_3\), 499.1378; found, 497.1343.

(E)-1,1-Diisopropoxy-4-(4-nitrophenyl)but-3-en-2-one (7d). The title compound was prepared via the general procedure from 4-nitrobenzaldehyde acetone 6e (191 mg, 1.0 mmol) and isopropanol 2i (1 mL). The product was isolated by flash chromatography using 5% ethyl acetate/hexane as an eluent; oil (251 mg, 82% yield); IR (KBr film): 3110, 2974, 2932, 2897, 1700, 1616, 1519, 1345, 1107, 1041 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.72 (d, J = 16.4 Hz, 1H), 7.53–7.31 (m, 5H), 7.03 (d, J = 16 Hz, 1H), 4.73 (s, 1H), 3.58–3.43 (m, 4H), 1.64–1.55 (m, 4H), 0.88 (t, J = 7.6 Hz, 6H) ppm; \(^{13}\)C{\(^1\)H}NMR (100 MHz, CDCl\(_3\)): \(\delta\) 194.3, 144.7, 133.6, 130.6, 128.8, 128.5, 120.8, 102.8, 69.2, 22.9, 10.5 ppm. HRMS (ESI) \(m/z\): [M + Na\(^+\)] calcd for C\(_{19}\)H\(_{20}\)O\(_2\)Na, 337.1189; found, 337.1190.

(E)-1,1-Dimethoxy-4-(p-tolyl)but-3-en-2-one (7b). The title compound was prepared via the general procedure from 4-methyl-benzaldehyde acetone 6b (160 mg, 1.0 mmol) and methanol 2b (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (210 mg, 78% yield); IR (KBr film): 2965, 2863, 1694, 1596, 1512, 1463, 1256, 1174, 1066 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.71 (d, J = 16.4 Hz, 1H), 7.43 (d, J = 8 Hz, 2H), 7.13 (d, J = 8 Hz, 2H), 6.96 (d, J = 16 Hz, 1H), 4.68 (s, 1H), 3.38 (s, 6H), 2.30 (s, 3H) ppm; \(^{13}\)C{\(^1\)H}NMR (100 MHz, CDCl\(_3\)): \(\delta\) 192.8, 144.2, 140.4, 130.7, 128.6, 127.7, 118.6, 102.6, 53.3, 20.5 ppm. HRMS (ESI) \(m/z\): [M + Na\(^+\)] calcd for C\(_{16}\)H\(_{19}\)O\(_2\), 243.0997; found, 243.0995.

(E)-4-Phenyl-1,1-diproproxybut-3-en-2-one (7a). The title compound was prepared via the general procedure from benzylidene acetone 6a (146 mg, 1.0 mmol) and 1-propanol 2c (1 mL). The product was isolated by flash chromatography using 1% ethyl acetate/hexane as an eluent; oil (225 mg, 86% yield); IR (KBr film): 3061, 3028, 2966, 2935, 2876, 1697, 1610, 1453, 1317, 1070 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.72 (d, J = 16.4 Hz, 1H), 7.53–7.31 (m, 5H), 7.03 (d, J = 16 Hz, 1H), 4.73 (s, 1H), 3.58–3.43 (m, 4H), 1.64–1.55 (m, 4H), 0.88 (t, J = 7.6 Hz, 6H) ppm; \(^{13}\)C{\(^1\)H}NMR (100 MHz, CDCl\(_3\)): \(\delta\) 194.3, 144.7, 133.6, 130.6, 128.8, 128.5, 120.8, 102.8, 69.2, 22.9, 10.5 ppm. HRMS (ESI) \(m/z\): [M + Na\(^+\)] calcd for C\(_{18}\)H\(_{20}\)O\(_2\)Na, 357.1367; found, 357.1368.
NMR (400 MHz, CDCl₃): δ 8.18 (d, J = 8.8 Hz, 2H), 7.72–7.66 (m, 3H), 7.14 (d, J = 16 Hz, 1H), 4.74 (s, 1H), 3.89–3.82 (m, 2H), 1.21 (d, J = 6 Hz, 6H), 1.11 (d, J = 6.4 Hz, 6H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 193.0, 147.5, 140.1, 139.9, 128.0, 123.4, 123.0, 99.6, 69.5, 21.9, 21.3 ppm. HRMS (ESI) m/z: [M + Na]⁺ calcd for C₁₀H₂₀O₃Na, 211.1317; found, 211.1316.

1,1-Dipropoxypropan-2-one (8a). The title compound was prepared via the general procedure from acetone 8a (58 mg, 1.0 mmol) and 1-propanol 2c (1 mL). The product was isolated by column chromatography using 1% ethyl acetate/hexane as an eluent; oil (172 mg, 67% yield); IR (KBr film): 2967, 2937, 2879, 1734, 1462, 1381, 1345, 1255, 1111, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.44 (s, 1H), 3.56–3.35 (m, 4H), 2.13 (s, 3H), 1.61–1.52 (m, 4H), 0.87 (t, J = 7.2 Hz, 6H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 203.4, 102.0, 68.4, 23.5, 21.9, 9.5 ppm. HRMS (ESI) m/z: [M + Na]⁺ calcd for C₁₀H₂₀O₃Na, 211.1317; found, 211.1316.

1,1-Dipropoxypropan-2-one (8b). The title compound was prepared via the general procedure from acetone 8a (58 mg, 1.0 mmol) and 1-hexanol 2e (1 mL). The product was isolated by column chromatography using 1% ethyl acetate/hexane as an eluent; oil (172 mg, 67% yield); IR (KBr film): 2967, 2937, 2879, 1734, 1462, 1381, 1345, 1255, 1111, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.44 (s, 1H), 3.58–3.39 (m, 4H), 2.12 (s, 3H), 1.57–1.50 (m, 4H), 1.30–1.21 (m, 12H), 0.81 (t, J = 6.4 Hz, 6H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 204.3, 103.0, 67.8, 31.5, 29.5, 25.6, 24.4, 22.5, 13.9 ppm. HRMS (ESI) m/z: [M + Na]⁺ calcd for C₁₀H₂₀O₃Na, 211.1317; found, 211.1309.

1,1-Dipropoxybutan-2-one (8c). The title compound was prepared via the general procedure from ethyl methyl ketone 8b (72 mg, 1.0 mmol) and 1-propanol 2c (1 mL). The product was isolated by column chromatography using 1% ethyl acetate/hexane as an eluent; oil (116 mg, 62% yield); IR (KBr film): 2968, 2938, 2878, 1730, 1601, 1461, 1381, 1258, 1103, 1074 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.48 (s, 1H), 3.55–3.36 (m, 4H), 2.54 (q, J = 7.6 Hz, 2H), 1.60–1.51 (m, 4H), 0.98 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.6 Hz, 6H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 207.0, 102.9, 69.4, 30.1, 22.8, 10.5, 6.9 ppm. HRMS (ESI) m/z: [M + Na]⁺ calcd for C₁₀H₂₀O₃Na, 211.1310; found, 211.1309.

1,1-Dioxypropentan-2-one (8d). The title compound was prepared via the general procedure from 2-pentanone 8e (86 mg, 1.0 mmol) and iso-propanol 2i (1 mL). The product was isolated by column chromatography using 1% ethyl acetate/hexane as an eluent; oil (116 mg, 62% yield); IR (KBr film): 2918, 2873, 1713, 1462, 1385, 1161, 1070 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.61 (s, 1H), 3.59–3.44 (m, 4H), 2.32–2.26 (m, 2H), 1.58–1.51 (m, 4H), 1.38–1.29 (m, 4H), 1.02–0.98 (m, 2H), 0.91–0.84 (m, 8H) ppm; ¹³C{¹H}NMR (100 MHz, CDCl₃): δ 205.3, 101.6, 66.1, 30.7, 18.2, 15.2, 10.8 ppm. HRMS (ESI) m/z: [M + Na]⁺ calcd for C₁₅H₃₀O₃Na, 251.1623; found, 251.1614.
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