Tandem Radical Addition and Cyclization of \(\varepsilon\)-Substituted \(\delta\)-Yne Ketimines

Marta Fernández and Ricardo Alonso*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

goraa@usc.es

Supporting Information

**General:** PYREX® vessels with a cold-finger internal condenser (see figure 1) were used for the photochemical reactions. Benzene was freshly distilled under argon from sodium/benzophenone. Purchased reagents, as well some solvents: 1,3-dioxolane (≥ 99%, GC), \(\alpha\)-xylene (98%, HPLC) and toluene (≥ 99.7%, GC, over molecular sieves) were used as received without further purification. Reaction mixtures were deoxygenated by bubbling dry argon (99.999%) for the indicated period. Thin-layer chromatography (TLC) was performed on precoated silica gel aluminium plates and components were visualized by observation under UV light, or by treating the plates with a solution of \((\text{NH}_4)_6\text{Mo}_7\text{O}_{24}.4\text{H}_2\text{O}\) (12.5 g) and \(\text{Ce(SO}_4)_2.4\text{H}_2\text{O}\) (5 g) in 10% aqueous \(\text{H}_2\text{SO}_4\) (500 mL), followed by heating. Flash column chromatography was performed on 230-400 mesh silica gel. Concentrations were carried out in a rotary evaporator. \(^1\text{H NMR were recorded at 300 or 400 MHz as indicated; }^{13}\text{C NMR at 75 and 100 MHz. Carbon types were determined from DEPT }^{13}\text{C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad signal.}

Figure 1: PYREX® vessel with a cold-finger internal condenser
Thermally-induced tandem radical addition-cyclization of Ib

(Table 1, entry 3 in the article)

To a deoxygenated (argon was bubbled for 10 min) solution of Ib (50.3 mg, 0.13 mmol) and AIBN (2.1 mg, 0.02 mmol) in refluxing toluene (0.9 mL), a solution of thiophenol (17.25 µL, 0.17 mmol) in toluene (0.7 mL) was slowly added via syringe (3.5 h). Once the addition finished, a second portion of AIBN (2.1 mg, 0.02 mmol) was added and the reaction mixture refluxed for 9.5 h. Solvent removal, followed by flash chromatography (EtOAc/hexane 5/95 → 35/65), afforded Ib (10.5 mg, 21%), IIb (9 mg, 14%) and IIIb (26.6 mg, 41%) as oils.

Spectroscopic data of IIb:

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.29-7.21 (m, 10H), 6.29 (s, 1H), 5.89 (d, $J = 3.6$ Hz, 1H), 5.09 (d, $J = 3.6$ Hz, 1H), 4.66 (s, 2H), 4.63 (d, $J = 3.7$ Hz, 1H), 4.38 (m, 1H), 3.46 (s, 3H), 3.09 (dd, $J = 18.4$ Hz, $J = 7.5$ Hz, 1H), 2.75 (dd, $J = 18.4$ Hz, $J = 9.8$ Hz, 1H), 2.10 (d, $J = 10.3$ Hz, 1H), 1.55 (s, 3H), 1.32 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 165.7, 151.5, 136.8, 135.1, 129.7, 129.1, 128.7, 128.4, 128.1, 127.0, 127.5, 113.9, 105.8, 88.1, 83.8, 78.7, 77.4, 72.0, 52.2, 41.0, 27.2, 27.0.

LRMS $m/z$ (%) 500 [33, (M+H)$^+$], 442 [40, (M+HOC(CH$_3$)$_2$)$^+$].

HRMS calculated for C$_{26}$H$_{30}$NO$_7$S (M+H)$^+$ 500.174299, found 500.175559.

IR (CsI) 3486, 3272, 3061-2988-2950, 1720, 1583 cm$^{-1}$.

Spectroscopic data of IIIb (isolated as a 55:45 mixture of geometric isomers):

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.40-7.21 (m, 20H), 6.53 (br s, 1H), 6.30 (br s, 1H), 5.81 (d, $J = 3.4$ Hz, 1H), 5.79 (d, $J = 3.4$ Hz, 1H), 5.18 (d, $J = 3.4$ Hz, 1H), 5.05 (d, $J = 3.4$ Hz, 1H), 4.77-4.55 (m, 5H), 4.40 (d, $J = 2.0$ Hz, 1H), 4.30 (m, 1H), 4.08 (m, 1H), 3.84 (s, 3H), 3.54 (s, 3H), 3.22 (dd, $J = 17.7$ Hz, $J = 7.3$ Hz, 1H), 3.42-2.31 (m, 2H), 2.21 (dd, $J = 17.2$ Hz, $J = 10.4$ Hz, 1H), 2.12 (d, $J = 10.5$ Hz, 1H), 1.75 (br s, 1H), 1.54 (s, 6H), 1.35 (s, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 168.0, 166.3, 142.2, 137.0, 136.9, 133.4, 133.0, 131.7, 130.1, 129.6, 129.2, 129.0, 128.6, 128.4, 128.3, 128.3, 128.2, 127.8, 127.1, 126.3, 113.7, 113.3, 105.6, 104.2, 88.6, 86.1, 82.6, 82.2, 77.9, 77.2, 76.9, 72.4, 71.4, 67.5, 52.3, 52.1, 40.5, 34.1, 27.4, 27.3, 27.2, 26.8.
A solution of **Ic** (76.6 mg, 0.18 mmol) in dry benzene (9.4 mL, 0.02 M) was deoxygenated by bubbling argon for 10 min. Thiophenol (20.5 µL, 0.19 mmol) was added and the mixture, maintained at T < 40 ºC, was externally irradiated with a 450 W Hanovia medium-pressure mercury lamp until **Ic** was consumed (TLC; t <sub>ν</sub> = 3 h). Solvent removal, followed by flash chromatography (EtOAc/hexane 10/90 → 20/80), afforded **IIc** as a white solid (73 mg, 75%) and **C** as oils (two chromatographic fractions, two diastereoisomers each; higher R <sub>f</sub> fraction: 6.1 mg, 6%, lower R <sub>f</sub> fraction: 6.3 mg, 6%).

**Spectroscopic data of IIc:**

**mp** = 168-170 °C (CH<sub>2</sub>Cl<sub>2</sub>/hexane).

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 7.43-7.16 (m, 15H), 6.06 (s, 1H), 5.85 (d, J = 3.3 Hz, 1H), 4.95 (d, J = 11.1 Hz, 1H), 4.81 (d, J = 11.1 Hz, 1H), 4.62 (d, J = 2.2 Hz, 1H), 4.34 (d, J = 3.3 Hz, 1H), 4.4-4.3 (m, 1H), 2.51 (dd, J = 16.8 Hz, J = 6.3 Hz, 1H), 2.35 (dd, J = 16.8 Hz, J = 10.1 Hz, 1H), 1.81 (d, J = 10.2 Hz, 1H), 1.55 (s, 3H), 1.24 (s, 3H).

**<sup>1</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)** δ 137.5, 136.7, 134.9, 134.5, 133.5, 131.8, 130.3, 128.9, 128.5, 128.3, 128.0, 127.7, 127.1, 113.6, 104.0, 83.2, 82.9, 76.2, 72.3, 67.4, 34.4, 27.2, 26.8.

**LRMS m/z (%) 518 [28, (M+H)<sup>+</sup>].**

Spectroscopic data of **C** (higher R <sub>f</sub>; two E/Z diastereoisomers):

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 7.43-7.16 (m, 30H), 6.88 (s, 1H), 6.85 (s, 1H), 5.80 (d, J = 4.4 Hz, 2H), 5.16 (dd, J = 4.4 Hz, J = 1.0 Hz, 1H), 5.00-4.94 (m, 5H), 4.93 (dd, J = 4.4 Hz, J = 1.1 Hz 1H), 4.53 (dd, J = 5.3 Hz, J = 1.0 Hz, 1H), 4.45 (m, 1H), 4.21 (m, 1H), 3.01 (dd, J = 14.5 Hz, J = 10.0 Hz, 1H), 2.88 (dd, J = 14.5 Hz, J = 10.5 Hz, 1H), 2.76 (d, J = 3.4 Hz, 1H), 2.53 (dd, J = 14.5 Hz, J = 2.6 Hz, 1H), 2.41 (d, J = 5.2 Hz, 1H),
2.30 (dd, $J = 14.5$ Hz, $J = 1.8$ Hz, 1H), 1.44 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H).

**LRMS** $m/z$ (%) 518 [10, (M+H)$^+$], 517 [13, (M)$^+$], 391 [41, (M-SPh-OH)$^+$].

Spectroscopic data of C (lower $R_f$, two $E$/Z diastereoisomers):

$^1$H NMR (CDCl$_3$, 400 MHz)  δ 7.36-7.25 (m, 30H), 6.74 (s, 2H), 5.86 (d, $J = 4.5$ Hz, 1H), 5.86 (d, $J = 4.4$ Hz, 1H), 5.19-5.16 (m, 3H), 5.13 (s, 2H), 4.98 (dd, $J = 2.7$ Hz, $J = 1.3$ Hz, 1H), 4.92 (dd, $J = 4.5$ Hz, $J = 1.3$ Hz 1H), 4.52 (dd, $J = 4.4$ Hz, $J = 1.1$ Hz, 1H), 4.32 (m, 1H), 4.08 (m, 1H), 2.57 (dd, $J = 14.3$ Hz, $J = 3.6$ Hz, 1H), 2.44-2.37 (m, 2H), 2.28 (dd, $J = 14.3$ Hz, $J = 9.7$ Hz, 1H), 2.18 (d, $J = 5.3$ Hz, 1H), 1.44 (s, 3H), 1.40 (s, 6H), 1.34 (s, 3H).

**LRMS** $m/z$ (%) 518 [1.7, (M+H)$^+$], 391 [9, (M-SPh-OH)$^+$].

**1,3-dioxolanyl radical-promoted tandem radical addition-cyclization of Ib**

(Scheme 2 in the article)

A solution of Ib (40 mg, 0.10 mmol) and benzophenone (19 mg, 0.10 mmol) in 1,3-dioxolane (2.5 mL, 0.04 M) was deoxygenated by bubbling argon for 10 min. The mixture, maintained at $T < 40$ ºC, was externally irradiated with a 450 W Hanovia medium-pressure mercury lamp until Ib was consumed (TLC; $t_{hv} = 2.25$ h). Solvent removal, followed by flash chromatography (EtOAc/hexane 35/65), afforded 3 as a colourless oil (31 mg, 65%).

$^1$H NMR (CDCl$_3$, 300 MHz)  δ 7.34-7.27 (m, 5H), 6.19 (s, 1H), 5.77 (d, $J = 3.4$ Hz, 1H), 5.42 (s, 1H), 5.25 (d, $J = 3.4$ Hz, 1H), 4.72 (d, $J = 11.1$ Hz, 1H), 4.56 (d, $J = 11.1$ Hz, 1H), 4.41 (d, $J = 1.9$ Hz, 1H), 4.13-4.09 (m, 1H), 4.05-3.89 (m, 4H), 3.81 (s, 3H), 2.54 (dd, $J = 17.4$ Hz, $J = 5.7$ Hz, 1H), 2.26 (dd, $J = 17.4$ Hz, $J = 10.5$ Hz, 1H), 1.90 (d, $J = 9.8$ Hz, 1H), 1.55 (s, 3H), 1.34 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz)  δ 168.6, 141.6, 137.1, 128.9, 128.5, 128.2, 127.7, 113.2, 104.2, 101.6, 82.5, 82.2, 76.8, 71.9, 67.1, 65.7, 52.1, 27.2, 26.8, 26.7.

**LRMS** $m/z$ (%) 464 [8, (M+H)$^+$], 391 [22, (M+H-dioxolanyl)$^+$].

**HRMS** calcd for C$_{23}$H$_{30}$NO$_9$ (M+H)$^+$ 464.192057, found 464.192424.
1H NMR (300 MHz)
1H NMR (400 MHz)
(higher R<sub>r</sub>, two E/Z diastereoisomers)
C (lower $R_f$, two E/Z diastereoisomers)