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Facile Synthesis of 4-Functionalized Cyclopentenones

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Abstract: 1-8-Diazabicyclo[5.4.0]undec-7-ene(DBU)-catalyzed Michael addition of nitroalkanes to dicyclopentadienone (**1**) followed by flash vacuum pyrolysis (FVP) provided a high-yielding synthesis of extremely pure 4-nitroalkyl cyclopentenones (**3**). The optimized Nef reaction of the nitro adducts (**2**) provided 4-ketoalkyl cyclopentenones (**5**) in the similar way.

Keywords: flash vacuum pyrolysis (FVP), Michael addition, Nef reaction, nitroalkanes

Because of their multifunctional properties, substituted cyclopentenones are versatile intermediates for the synthesis of several bioactive natural products containing five-membered rings.[1] 4-Substituted cyclopentenones, especially 4-nitroalykl cyclopentenones, could be considered the more important intermediates because a nitroalkyl group provides a new reaction center in addition to their existing five reactive carbon centers. Although the Pauson–Khand[2] reaction has been extensively used for the synthesis of cyclopentenones using alkenes, alkynes, and high-pressure carbon monoxide, newer preparative methods are still being developed.[3] In recent years, Klunder and coworkers have shown the utility of flash vacuum pyrolysis (FVP) for the synthesis of substituted cyclopentenones.[4] As a part of our current study[5] directed toward synthesis of stealthins and kinamycin antibiotics, in which

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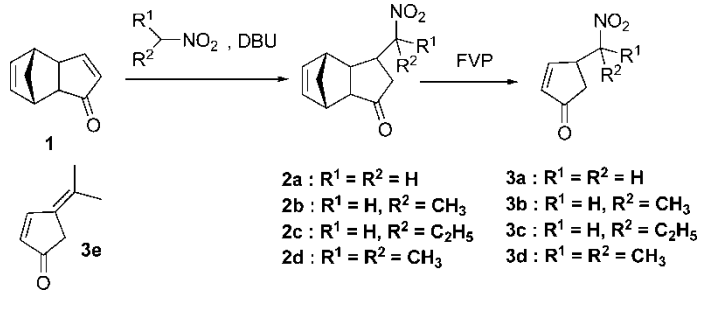
cyclopentenone moieties are embedded, we successfully synthesized 4-nitromethyl cyclopentenones in excellent yield using FVP as a key step. Therefore, we decided to generalize the method. Herein, we report a new and general synthesis of 4-nitroalkyl cyclopentenones (**3**) as well as a general synthesis of 4-(1-oxoalkyl)cyclopentenones (**4**).

RESULTS AND DISCUSSION

Dicyclopentadineone **1** was prepared on a large scale (~50 g) in two steps from commercially available dicyclopentadiene according to the literature method.[6] Treatment of the enone **1** with 15-fold excess of nitromethane in the presence of DBU provided **2a** in high yield (Scheme 1). All other bases (e.g., NaOH, KOH, NaOEt, Et_3N, $^{i}Pr_2NH$, $^{t}BuOK$, and $^{t}BuOLi$) examined in the place of DBU resulted in either very poor yields of the products or no products. When the nitro adduct **2a** was subjected to FVP at 400°C and 0.01 Torr., the expected cyclopentenone **3a** was obtained in excellent yield (>90%). Two signals of olefinic protons in the ^1H NMR spectrum and two strong peaks in the IR spectrum at 1711 cm^{-1} and 1548 cm^{-1} corresponding to carbonyl and nitro groups left no doubt about the structure of the compound **3a**. Compounds **2b, 2c**, and **2d** were similarly prepared by treatment of enone **1** with an excess of the respective nitroalkanes (**6**). Compounds **2b** and **2c**, and their corresponding thermolyzed products **3b** and **3c** were obtained as inseparable mixtures of two respective diastereomers. ^{13}C NMR spectra of all the compounds showed two sets of signals corresponding to each carbon. When the compound **2d** was subjected to FVP at 450°C and 0.01 Torr., the corresponding thermolyzed product **3d** was obtained in 70% yield along with **3e** (15%), which was deposited in the different regions of the collection tube. The unusual formation of the second compound **3e** could be explained by the loss of HNO_2 followed by retro Diels–Alder reaction of **2d**. Although organonitro compounds tend to detonate at high temperatures, compounds **3a**–**3d** showed no sign of instability to heat.



Scheme 1.

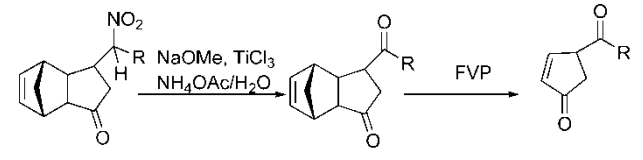
The Nef reaction[7] (i.e., the reaction for the conversion of a nitroalkyl to carbonyl functionality) is a well-studied reaction. However, the outcome of the reaction with respect to yield of a keto product is highly dependent on the nature of reagents and reaction conditions. A reliable prescription is still lacking in the literature. After scrutiny of several reagents, buffered $TiCl_3$[8] was found to be the most suitable for the present study, and it was successfully utilized for the conversion of nitro compounds **2a**, **2b**, and **2c** to the respective keto compounds (Scheme 2). Both the compounds **4b** and **4c** could be purified by silica-gel column chromatography. Compound **4a** could not be fully purified. It was sufficiently pure for spectral characterization. The appearance of a signal at δ10.1 ppm in the ^{1}H NMR spectrum of compound **4a** was indicative of its formation, but it was too unstable for further characterization. Flash vacuum pyrolysis of **4b** and **4c** at 350°C and 0.01 Torr. provided the expected cyclopentenones **5b** and **5c** in good yields.

In conclusion, we have described an easy preparation of 4-functionalized cyclopentenones from easily accessible starting materials. Although the route is easily conceivable on the basis of well-established retro Diels–Alder reactions, the finding on the use of DBU for the successful Michael additions is critically important.

EXPERIMENTAL

General

^{1}H NMR spectra were recorded at 200 MHz (Brucker) solution for ^{2}H chloroform with tetramethylsilane as the internal standard. IR spectra were obtained on a Perkin-Elmer instrument, model 883, using KBr pellets (for solids) or neat (for liquids). Melting points were determined in open capillary tubes and are uncorrected. All solvents used for the reactions were purified before use.



2a : R = H
2b : R = CH_3
2c : R = C_2H_5

4a : R = H
4b : R = CH_3
4c : R = C_2H_5

5b : R = CH_3
5c : R = C_2H_5

Scheme 2.

2,3,3a,4,7,7a-Hexahydro-4,7-methano-3-nitromethyl-1*H*-indene-1-one (2a)

To a stirred solution of 3a,4,7,7a-tetrahydro-4,7-methano-1*H*-inden-1-one **1** (2.5 g, 10.25 mmol) and nitromethane (15 eq.), DBU (3 drops) was added at 0°C and allowed to stir at room temperature overnight. The reaction mixture was diluted with diethyl ether (150 mL) and washed with 5% HCl, water, and brine. The organic layer was then dried (Na_2SO_4) and concentrated to provide a crude product. The crude was purified by chromatography to furnish **2a** as an oil (1.31 g, 67%). ^{1}H NMR (200 MHz): δ 6.21 (brs, 2H, CH═CH), 4.48–4.26 (m, 2H, CH_2NO_2), 3.24–3.22 (m, 1H, ring-H), 3.1 (brs, 1H, ring-H), 3.05–2.9 (m, 1H, ring-H), 2.8–2.7 (m, 1H, ring-H), 2.6–2.48 (m, 1H, CH-CH_2NO_2), 2.4–1.97 (m, 2H, CH_2-O), 1.61 (Ad, 1H, $J = 8.6$ Hz, CH_2-bridge), 1.4 (ABq, 1H, $J = 8.6$ Hz, CH_2-bridge); ^{13}C NMR (50 MHz): δ 216.3, 136.9, 134.6, 79.8, 54.7, 52.2, 46.9, 46.4, 46, 44.6, 35.2; IR (cm^{-1}): 1733, 1549, 1381, 1190, 735; MS(m/z): 207 (M+).

4-(1-Nitromethyl)cyclopent-1-enone (3a)

This compound was prepared as a colorless oil in 95% yield by FVP of **2a**, at 450°C, 0.01 mm. ^{1}H NMR (200 MHz): δ7.59–7.55 (m, 1H, CH═), 6.34–6.30 (m, 1H, CH═), 4.51–4.43 (m, 2H, CH_2-NO_2), 3.75–3.70 (m, 1H, ring-H), 2.67 (ABq, 1H, $J = 18.8$, 2.6 Hz, CH_2CO), 2.18 (ABq, 1H, $J = 18.8$, 2.6 Hz, CH_2CO); ^{13}C NMR (50 MHz): δ 206.31, 161.18, 136.46, 77.39, 39.24, 38.07; IR (cm^{-1}): 1711, 1548, 1381, 1179.

2,3,3a,4,7,7a-Hexahydro-4,7-methano-3-(1-nitroethyl)-1*H*-indene-1-one (2b)

This compound was prepared as a colorless oil in 84% yield from **1** and nitromethane following the procedure adopted for the preparation of compound **2a**. ^{1}H NMR (200 MHz): (mixture of diastereomers) δ 6.19–6.17 (m, 2H, CH═CH), 4.54-4.43 (m, 1H, CH-NO_2), 3.20 (brs, 1H, ring-H), 3.03–2.94 (m, 2H, ring-H), 2.80–2.68 (m, 1H, ring-H), 2.32–2.09 (m, 3H, CH_2-CO), 1.67-1.41 (m, 5H, bridge-CH_2, CH_3); ^{13}C NMR (50 MHz): δ (216.75, 216.55), (136.97, 136.72), (134.91, 134.60), (87.43, 86.88), (55.14, 54.96), (52.24, 52.22), (47.11, 47.03), (46.01, 45.90), (45.37, 44.55), (44.46, 44.10), (41.54, 41.37), (17.45, 16.81); IR (cm^{-1}): 1730, 1541, 1132, 730.

4-(1-Nitroethyl)-cyclopent-2-enone (3b)

This compound was prepared as a colorless oil in 95% yield by FVP of **2b.** ^{1}H NMR (200 MHz): (mixture of diastereomers) δ 7.59–7.45 (m, 1H, CH═),

6.30–6.25 (m, 1H, CH═), 4.65–4.56 (m, 1H, CH-NO_2), 3.58–3.49 (m, 1H, ring-H), 2.53 (dd, $J = 19.0$, 6.8 Hz, 1H, CH_2), 2.23–2.10 (m, 1H, CH_2), 1.58–1.52 (m, 3H, CH_3); ^{13}C NMR (50 MHz): (206.25, 206.12), (161.09, 160.74), (136.81, 136.36), (84.58, 84.43), (44.98, 44.78), (37.21, 36.56), (16.45, 16.29); IR (cm^{-1}): 2989, 1716, 1546, 1398, 1185.

2,3,3a,4,7,7a-Hexahydro-4,7-methano-3-(1-nitropropyl)-1*H*-indene-1-one (2c)

This compound was prepared as a colorless oil in 84% yield from **1** and 2-nitropropane following the procedure adopted for the preparation of compound **2a**. ^{1}H NMR (200 MHz): (mixture of diastereomers) δ 6.21–6.16 (m, 2H, CH═), 4.37–4.26 (m, 1H, CH-NO_2), 3.18 (brs, 1H, ring-H), 3.03–2.91 (m, 2H, ring-H), 2.82–2.73 (m, 2H, ring-H), 2.27–2.11 (m, 2H, CH_2CO), 2.06–1.82 (m, 2H, CH_2-CH_3), 1.71–1.40 (m, 2H, CH_2), 1.04–0.92 (m, 3H, CH_3); ^{13}C NMR (50 MHz): δ (216.50, 216.28), (137.16, 136.97), (135.11, 134.63), (94.81, 94.35), (55.12, 54.94), 52.34, (47.12, 47.03), (45.85, 45.73), 45.44, (44.98, 44.59), (40.74, 40.62), (25.48, 25.02), (10.35, 10.20); **MS** (m/z): 236 ($M^+ + 1$).

4-(1-Nitropropyl)-cyclopent-2-enone (3c)

This compound was prepared as an odorless oil in 94% yield by FVP of **2c**. ^{1}H NMR (200 MHz): δ 7.62–7.43 (m, 1H, CH═), 6.35–6.29 (m, 1H, CH═), 4.49–4.28 (m, 1H, CH-NO_2), 3.60–3.42 (m, 1H, ring-CH), 2.49–1.76 (m, 4H, CH_2CO, CH_2CH_3), 1.03 (t, 3H, J = 7.3 Hz, CH_3); IR (cm^{-1}): 1716, 1545, 1163, 1063, 795.

2,3,3a,4,7,7a-Hexahydro-4,7-methano-3-(2-nitropropyl)1*H*-indene-1-one (2d)

This compound was prepared as white solid in 88% yield from **1**, following the procedure adopted for the preparation of compound **2a**. Mp: 80°C; ^{1}H NMR (200 MHz): δ 6.26–6.20 (m, 2H, CH═CH), 3.21–3.19 (m, 1H, ring-H), 3.01–2.91 (m, 2H, ring-H), 2.74–2.65 (m, 1H, ring-H), 2.49–2.38 (m, 1H, ring-H), 2.19-2.10 (m, 2H, CH_2, CH_2CO), 1.56 (s, 6H, CH_3), 1.48–1.41 (m, 2H, bridge-CH_2); ^{13}C NMR (50 MHz): δ 217.77, 136.76, 134.69, 90.96, 55.24, 52.16, 47.67, 46.51, 45.83, 44.18, 43.43, 24.33, 22.89; IR (cm^{-1}) 1729, 1524, 1344, 1137, 734.

4-(2-Nitropropyl)-cyclopent-2-enone (3d)

This compound was prepared as a white solid in 70% yield by FVP of **2d**. Mp: 79°C; ^{1}H NMR (200 MHz): 7.52–7.47 (m, 1H, CH═), 6.34–6.30 (m, 1H,

CH═), 3.72–3.63 (m, 1H, ring-H), 2.53 (ABq, 1H, $J = 19$, 6.8 Hz, CH_2CO), 2.14 (ABq, 1H, $J = 19$, 2.8 Hz, CH_2CO), 1.60 (s, 3H, CH_3), 1.49 (s, 3H, CH_3); ^{13}C NMR (50 MHz): δ 206.38, 161.08, 136.69, 89.14, 49.52, 36.86, 23.60, 23.26; IR (cm^{-1}): 1707, 1528, 1348, 1191, 845, 734.

4-(2-Propylidine)-cycolpent-2-enone (3e)

This compound was formed as a white solid in 15% yield during the synthesis of compound **3d**. Mp: 81°C. ^1H NMR (200 MHz): δ 8.98 (d, 1H, $J = 5.6$ Hz, CH═), 6.16 (d, 1H, $J = 5.6$ Hz, CH═), 2.88 (s, 2H, CH_2CO), 1.60 (s, 3H, CH3), 1.49 (s, 3H, CH_3); IR (cm^{-1}): 1710, 1192, 773.

2,3,3a,4,7,7a-Hexahydro-4,7-methano-3(1-oxoethyl)-1*H*-indene-1-one (4b)

A solution of nitro compound **2b** (0.5 g, 2.26 mmol) in methanol (35 mL) was treated sequentially with sodium methoxide (6.84 mmol) and a solution of titanium trichloride (15% w/v, 13.2 mL) in ammonium acetate (6 g in 13.2 mL of water). The mixture was stirred under nitrogen for 30 min and with external cooling (ice water). Diethyl ether (50 mL) and brine (35 mL) was added, and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 35 mL). The combined organic layer was washed with aqueous sodium bicarbonate (3 × 60 mL), water (60 mL), and brine (40 mL) and then dried (Na_2SO_4) and concentrated to provide a crude product, which was purified by column (silica-gel) chromatography to give pure product as an oil (0.35 g, 83% yield). ^1H NMR (200 MHz): δ 6.20 (brs, 2 H, CH═CH), 3.21 (brs, 1H, ring-H), 3.13 (brs, 1H, ring-H), 3.04–2.95 (m, 2H, ring-H), 2.70–2.65 (m, 1H, CH_2CO), 2.58–2.54 (m, 1H, CH_2-CO), 2.23 (s, 3H, CH_3), 2.12–2.08 (m, 1H, CH_2-CO), 1.64 (ABd, 1H, $J = 8.4$ Hz, CH_2), 1.49 (ABd, 1H, $J = 8.4$, CH_2); ^{13}C NMR (50 MHz): δ 216.95, 207.16, 137.31, 134.00, 54.11, 52.25, 49.56, 46.98, 46.00, 44.36, 42.34, 28.42; IR (cm^{-1}) 2973, 1729, 1354, 1175.

4-(1-Oxoethyl)-cyclopent-2-enone (5b)

This compound was prepared as a colorless oil in 78% yield by FVP of **4b**. ^1H NMR (200 MHz): δ 7.67–7.65 (dd, $J = 12$, 3 Hz, 1H, CH═), 6.24–6.22 (dd, $J = 12$, 2, 1H, CH═), 3.93–3.86 (m, 1H, ring-H), 2.43–2.40 (m, 2H, ring-H), 2.35–2.26 (m, 3H, CH_3); ^{13}C NMR (50 MHz): δ 207.43, 294.19, 160.00, 135.24, 54.77, 35.89, 28.44; IR (cm^{-1}): 1722, 722.

2,3,3a,4,7,7a-Hexahydro-4,7-methano-3-(1-oxopropyl)-1 *H*-inden-1-one (4c)

This compound was prepared as a colorless oil in 81% yield from **3c**, following the procedure adopted for the preparation of compound **4b**. ^{1}H NMR (200 MHz): δ 6.29–6.25 (m, 2H, CH═CH), 3.23 (brs, 1H, ring-H), 3.13 (brs, 1H, ring-H), 3.01-2.98 (m, 2H, ring-H), 2.62–2.48 (m, 3H, ring-H, CH_2CO), 2.39–2.34 (m, 2H, ring-CH_2CO), 1.64 (ABd, 1H, $J = 7.9$ Hz, ring-CH_2), 1.51–1.47 (ABd, 1H, $J = 7.9$ Hz, ring-CH_2), 1.10 (t, 3H, $J = 7.1$ Hz, CH_3); ^{13}C NMR (50 MHz): δ 218.06, 211.06, 137.27, 134.17, 54.25, 52.30, 48.52, 47.03, 46.05, 44.83, 42.78, 34.78, 27.84; IR (cm^{-1}): 2976, 1727, 1454, 1118, 1123, 735.

4-(1-Oxopropyl)-cyclopent-2-enone (5c)

This compound was prepared as colorless oil in 74% yield by FVP of **4c**. ^{1}H NMR (200 MHz): δ 7.68–7.64 (m, 1H, CH═), 6.25–6.21 (m, 1H, CH═), 3.98–3.91 (m, 1H, ring-H), 3.14 (dd, 1H, $J = 8.8$, 2.5 Hz, ring-CH_2CO), 2.67–2.48 (m, 3 H, CH_2CO, ring-CH_2-CO), 1.08 (t, 3H, $J = 7.3$ Hz, CH_3); ^{13}C NMR (50 MHz): 207.50, 207.09, 160.22, 135.10, 53.71, 36.11, 34.72, 7.56; IR (cm^{-1}): 2980, 2934, 1716, 1690, 1189, 779.

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