A New Stereoselective Synthesis of (*E*)-α,β-Unsaturated-γ-dicarbonyl Compounds by the Henry Reaction

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(*E*)-Enediones are valuable intermediates for the synthesis of important molecules such as prostaglandins,[1] rethrolones,[2] perfumes,[3] pheromones,[4] macrocycles,[5] and other natural products. Considerable attention has been paid to methods for the synthesis of these compounds, in particular the ring cleavage of 2-mono or 2,5-disubstituted furans. This transformation can be performed by several different oxidative methods,[4a,5-11] but these methods suffer from certain drawbacks, such as regioselective alkylation of the furan before the ring cleavage, the use of potentially explosive reagents, severe reaction conditions, and formation of mixtures of (*E*)- and (*Z*)-isomers or exclusive formation of the (*Z*)-isomer, which requires a strong acid for isomerization to the (*E*)-compound. The preparation of the (*E*)-enedione system *via* alternative methods thus is important.

Nitroalkanes have proved useful in complex organic syntheses because of the many possible transformations of the nitro functionality and perhaps more importantly because of the variety of carbon–carbon bond-forming reactions that proceed under very mild conditions.[12-18] The nitroaldol (Henry)[19] reaction and its variants have been used extensively in carbon–carbon bond formation.[20] Because of the mild conditions required, it is not surprising to find that this reaction has been applied broadly in the synthesis of many important molecules.[15,18-30] As an extension of the nitroaldol reaction, we have invented a new stereoselective method for the transformation of nitroaldols into (*E*)-enediones.

Scheme 1

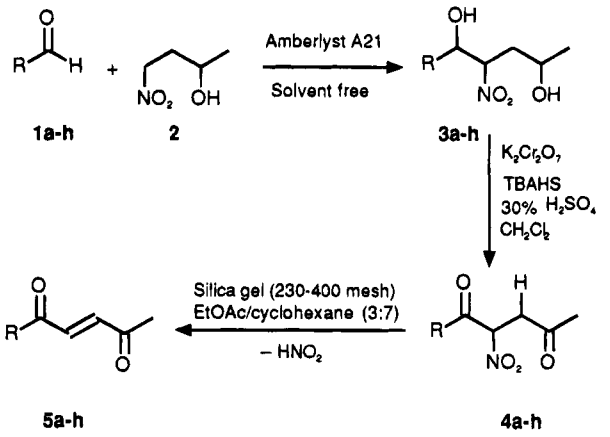

Table 1. Nitroaldol Reaction (3) and Preparation of (*E*)-Enediones 5

compd	R	nitroalkanol 3 yield (%)	enedione 5 yield (%) from 3
a	Me	75	53
b	i-Pr	80	45
c	n-pentyl	65	47
d	n-decyl	86	58
e	cyclohexyl	78	58
f	$PhCH_2CH_2$	80	70
g	$CH_3(CH_2)_7CH\overset{Z}{=}CH(CH_2)_7$	70	58
h	$CH_3(CH_2)_4CH(NO_2)(CH_2)_2$	82	65

Our procedure starts (Scheme 1) with a nitroaldol reaction between aldehydes **1** and nitro alcohol[31] **2** in the presence of Amberlyst A 21 and in the absence of solvent to give nitro diols **3** in good yields (65–86%). Potassium dichromate oxidation of **3** under phase-transfer conditions affords crude α-nitro ketones **4**. Vigorous stirring (20 h) of **4** in a mixture of cyclohexane/EtOAc (7:3) and silica gel (0.040–0.063 mm) and subsequent flash chromatography[32] effect the elimination of nitrous acid and afford α,β-unsaturated-γ-dicarbonyl derivatives **5** exclusively as the (*E*)-isomers in 45–70% yields from **3**.

It is important to point out that this procedure does not affect a labile functional group such as a (*Z*)-C–C double bond (see **5g**), whereas most of the reagents proposed for the ring cleavage of furans can produce modifications of the double bond such as isomerization (PCC),[33] epoxidation (peracids),[34] and addition reactions

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(31) Compound **2** has been prepared in 82% yield by sodium borohydride reduction of the corresponding β-nitro ketone. Other 3-nitroalkanols can be obtained in the same way from 3-nitro carbonyl derivatives: (a) Miyiakoshi, T.; Saito, S.; Kumanotani, J. *Chem. Lett.* **1981**, 1677. (b) Ohrlein, R.; Schwab, W.; Ehrler, R.; Jager, V. *Synthesis* **1986**, 535. (c) Reference 21.
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and/or oxidations (bromine).[35] A nitro group that is not α to the alcohol (see **5h**) is preserved. Since this important functionality facilities a variety of carbon–carbon bond-forming processes, and a wide range of efficient methods for its transformation into other functionalities are available in the literature,[12,15,17,18] its presence in the molecule offers important opportunities for further elaboration.

In conclusion, a new stereoselective synthesis of (*E*)-enediones has been realized. Because the method is simple, mild, and cheap and requires readily available starting materials, it can be considered an attractive and useful alternative to the existing ones, especially for the synthesis of important molecules such as natural products where the preservation of the stereoisomeric purity of a C—C double bond is the most important goal. This method also represents an additional important utilization of the Henry reaction in organic synthesis.[20]

Experimental Section

General. All ^{1}H NMR spectra were recorded in $CDCl_3$ or C_6D_6 at 300 MHz. *J* values are given in hertz. Reaction progress was monitored by TLC. Products **3** and **5** were purified by flash chromatography[32] on Merck silica gel (0.040–0.063 mm). Aldehyde **1h** was prepared by the reported[36] method. Nitro alcohol **2** has been prepared from 1-nitrobutan-3-one by sodium borohydride reduction.[31]

General Procedure for the Synthesis of Nitro Alcohol (3). A 100 mL two-necked flask equipped with a mechanical stirrer was charged with nitro compound **2** (2.38 g, 20 mmol) and cooled with an ice–water bath. Aldehyde **1** (20 mmol) was added, and the mixture was stirred for 10 min. Amberlyst A21 was added, and stirring was continued for 15 h. The Amberlyst was washed with CH_2Cl_2 (3 × 50 mL). The filtered extract was evaporated, and crude nitro alcohol **3** was either purified by flash chromatography (cyclohexane/EtOAc/EtOH, 6:3.5:0.5) or used without purification for the next step.

3-Nitrohexane-2,5-diol (3a): yield 75%; oil; IR (cm^{-1}, neat) 3360, 1545; ^{1}H NMR ($CDCl_3$) δ 1.15–1.4 (m, 6H), 1.95 (m, 2H), 3.65–4.2 (m, 2H), 4.65–4.9 (m, 1H). Anal. Calcd for $C_6H_{13}NO_4$: C, 44.17; H, 8.03; N, 8.58. Found: C, 44.38; H, 8.2; N, 8.43.

2-Methyl-4-nitroheptane-3,6-diol (3b): yield 80%; oil; IR (cm^{-1}, neat) 3360, 1545; ^{1}H NMR ($CDCl_3$) δ 0.8–1.1 (m, 6H), 1.28 (m, 3H), 1.6–2.4 (m, 3H), 3.45–3.95 (m, 2H), 4.7–5.05 (m, 1H). Anal. Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: C, 50.38; H, 9.09; N, 7.19.

4-Nitrodecane-2,5-diol (3c): yield 65%; oil; IR (cm^{-1}, neat) 3380, 1545; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J* = 6.65 Hz), 1.1–2.4 (m, 13H), 3.65–4.2 (m, 2H), 4.5–4.9 (m, 1H). Anal. Calcd for $C_{10}H_{21}NO_4$: C, 54.77; H, 9.65; N, 7.32. Found: C, 54.89; H, 9.8; N, 7.2.

4-Nitropentadecane-2,5-diol (3d): yield 86%; oil; IR (cm^{-1}, neat) 3380, 1545; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.2 Hz), 1.1–2.45 (m, 23H), 3.7–4.2 (m, 2H), 4.6–4.9 (m, 1H). Anal. Calcd for $C_{15}H_{31}NO_4$: C, 62.25; H, 10.8; N, 4.84. Found: C, 62.4; H, 10.94; N, 4.68.

1-Cyclohexyl-2-nitropentane-1,4-diol (3e): yield 78%; IR (cm^{-1}, neat) 3360, 1540; ^{1}H NMR ($CDCl_3$) δ 0.9–2.4 (m, 16H), 3.6–4.1 (m, 2H), 4.7–5.1 (m, 1H). Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.33; H, 9.27; N, 5.89.

1-Phenyl-4-nitroheptane-3,6-diol (3f): yield 80%; IR (cm^{-1}, neat) 3360, 1540; ^{1}H NMR ($CDCl_3$) δ 1.2 (m, 3H), 1.6–3.0 (m, 6H), 3.7–4.2 (m, 2H), 4.7–4.9 (m, 1H), 7.1–7.4 (m, 5H). Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.8; H, 7.69; N, 5.39.

(*Z*)-19-Nitro-9-docosene-18,21-diol (3g): yield 70%; oil; IR (cm^{-1}, neat) 3400, 1540; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.3 Hz), 1.18–2.4 (m, 33H), 3.7–4.2 (m, 2H), 4.7–4.9 (m, 1H), 5.3–5.45 (m, 2H). Anal. Calcd for $C_{22}H_{43}NO_4$: C, 68.53; H, 11.24; N, 3.63. Found: C, 68.2; H, 11.07; N, 3.8.

4,8-Dinitrotridecane-2,5-diol (3h): yield 82%; oil; IR (cm^{-1}, neat) 3400, 1540; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3H, *J* = 6.8 Hz), 1.2–2.3 (m, 17H), 3.7–4.15 (m, 2H), 4.4–4.68 (m, 1H), 4.71–4.89 (m, 1H). Anal. Calcd for $C_{13}H_{26}N_2O_6$: C, 50.97; H, 8.55; N, 9.14. Found: C, 51.31; H, 8.39; N, 8.97.

General Procedure for the Preparation of Enediones 5. To a mechanically stirred solution of **3** (10 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.34 g, 1 mmol) in CH_2Cl_2 (30 mL) at −10 °C were added 30% sulfuric acid (15 mL) and potassium dichromate (4.12 g, 14 mmol) slowly and simultaneously. After the mixture stirred for 2 h at −10 °C, the layers were separated. The organic phase was dried (Na_2SO_4) and passed through a pad of Florisil. After evaporation, crude[37] α-nitro ketone **4** was vigorously stirred in a mixture of cyclohexane/EtOAc (7:3, 30 mL) and silica gel (0.040–0.063 mm, 10 g) and then purified by flash chromatography under the same conditions to give pure (*E*)-enedione **5**.

(*E*)-3-Hexene-2,5-dione (5a): yield 53%; oil; IR (cm^{-1}, neat) 1660; ^{1}H NMR (C_6D_6) δ 3.4 (s, 6H), 6.35 (d, 1H, *J* = 16.2 Hz), 6.43 (d, 1H, *J* = 16.2 Hz). Anal. Calcd for $C_6H_8NO_2$: C, 64.27; H, 7.19. Found: C, 64.39; H, 7.31.

(*E*)-6-Methyl-3-heptene-2,4-dione (5b): yield 45%; bp_{130} 100 °C (Kugelrohr); IR (cm^{-1}, neat) 1665; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 6H, *J* = 7.1 Hz), 2.38 (s, 3H), 2.9 (m, 1H), 6.85 (d, 1H, *J* = 16.2 Hz), 6.96 (d, 1H, *J* = 16.2 Hz). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.7; H, 8.79.

(*E*)-3-Decene-2,5-dione (5c): yield 47%; mp 47–48 °C; IR (cm^{-1}, KBr) 1665; ^{1}H NMR (C_6D_6) δ 0.86 (t, 3H, *J* = 7.03 Hz), 1–1.15 (m, 6H), 1.69 (s, 3H), 2.05 (t, 2H, *J* = 7.16 Hz), 6.45 (d, 1H, *J* = 16.35 Hz), 6.55 (d, 1H, *J* = 16.35 Hz). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.21; H, 9.73.

(*E*)-3-Pentadecene-2,5-dione (5d): yield 58%; mp 65–66 °C; IR (cm^{-1}, KBr) 1655; ^{1}H NMR (C_6D_6) δ 0.9 (t, 3H, *J* = 6.9 Hz), 1.1–1.65 (m, 16H), 1.69 (s, 3H), 2.1 (t, 2H, *J* = 7.33 Hz), 6.45 (d, 1H, *J* = 16.48 Hz), 6.55 (d, 1H, *J* = 16.48 Hz). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.73; H, 11.12.

(*E*)-5-Cyclohexyl-3-pentene-2,5-dione (5e): yield 58%; mp 71–73 °C; IR (cm^{-1}, KBr) 1655; ^{1}H NMR ($CDCl_3$) δ 1.2–1.95 (m, 10H), 2.38 (s, 3H), 2.55–2.75 (m, 1H), 6.85 (d, 1H, *J* = 16.2 Hz), 6.96 (d, 1H, *J* = 16.2 Hz). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.3; H, 8.95. Found: C, 73.43; H, 9.08.

(*E*)-7-Phenyl-3-heptene-2,5-dione (5f): yield 70%; mp 70–72 °C; IR (cm^{-1}, KBr) 1655; ^{1}H NMR (C_6D_6) δ 1.67 (s, 3H), 2.3 (t, 2H, *J* = 7 Hz), 2.78 (t, 2H, *J* = 7.1 Hz), 6.32 (d, 1H, *J* = 16.3 Hz), 6.45 (d, 1H, *J* = 16.3 Hz), 6.98–7.2 (m, 5H). Anal. Calcd for $C_{13}H_{14}O_2$: C, 72.2; H, 6.98. Found: C, 77.32; H, 7.12.

(*3E,13Z*)-3,13-Docosadiene-2,5-dione (5g): yield 58%; mp 64–65 °C; IR (cm^{-1}, KBr) 1668; ^{1}H NMR (C_6D_6)[38] δ 0.9 (m, 3H), 1.1–2.25 (m, 28H), 1.7 (s, 3H), 5.5–5.98 (m, 2H), 6.45 (d, 1H, *J* = 16.34 Hz), 6.57 (d, 1H, *J* = 16.34 Hz). Anal. Calcd for $C_{22}H_{38}O_2$: c, 78.99; H, 11.45. Found: C, 79.2; H, 11.62.

(*E*)-8-Nitro-3-tridecene-2,5-dione (5h): yield 65%; oil; IR (cm^{-1}, film) 1540, 1670; ^{1}H NMR (C_6D_6) δ 0.8 (t, 3H, *J* = 6.5 Hz), 0.9–2.08 (m, 12H), 1.72 (s, 3H), 4.2 (m, 1H, *J* = 4.7 Hz), 6.3 (d, 1H, *J* = 16.32 Hz), 6.45 (d, 1H, *J* = 16.32 Hz). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.00; H, 8.48; N, 5.62.

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(37) Crude nitro ketones **4** have been identified by IR and ^{1}H NMR spectroscopy.
(38) The vinyl multiplet (δ 5.5–5.98) has been compared with those of (*E*)- and (*Z*)-4-heptenal **1g**.