Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 05 Dec 2006.

To cite this article: Richard A. Bunce & J. Travis Parker (1992) An improved Synthesis of Methyl (E)-5-Nitro-2-Pentenoate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:3, 377-380, DOI: 10.1080/00397919208055414

To link to this article: http://dx.doi.org/10.1080/00397919208055414

SYNTHETIC COMMUNICATIONS, 22(3), 377-380 (1992)

AN IMPROVED SYNTHESIS OF METHYL (*E*)-5-NITRO-2-PENTENOATE

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Abstract: A two-step synthesis of methyl (*E*)-5-nitro-2-pentenoate involving addition of nitrous acid to acrolein followed by Wittig olefination is described. The preparation can be routinely carried out on a 0.1 mole scale to afford the title compound in 45-50% overall yield as a 92:8 mixture of the *E*:*Z* double bond isomers.

A synthetic study involving the development of tandem reaction processes for the preparation of heterocyclic ring systems required multigram quantities of methyl (*E*)-5-nitro-2-pentenoate (**3**). Nitro ester **3** has previously found use as an important building block in the synthesis of several tropane alkaloids.[2] An efficient route to this highly functionalized molecule would advance our project and lead to its further use in the synthesis of complex biologically active targets.

The original literature synthesis[2] of **3** involved seven steps, used a relatively expensive starting material and, assuming optimum results, proceeded in only 17.5% overall yield. Subsequent work[3,4] described the preparation of several intermediates from the earlier synthesis and eliminated the need for expensive starting materials but the low-yield conversion of methyl (*E*)-5-bromo-2-pentenoate to **3** in the last step remained a problem. We wish to report a two-step synthesis of methyl (*E*)-5-nitro-2-pentenoate which 1) considerably decreases the number of laboratory operations and shortens the time required to prepare the compound, 2) avoids low-yield steps associated with earlier syntheses and 3) proceeds reproducibly in 45-50% overall yield on a 0.1 mole (or larger) scale.

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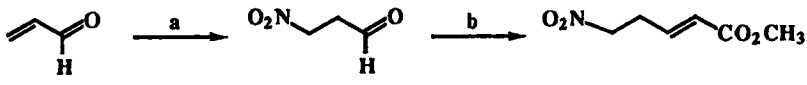

1 2 3

(a) $NaNO_2$, CH_3CO_2H, THF, 0°C, 3h, 54-58%; (b) $Ph_3P{=}CHCO_2CH_3$, PhH, 60°C, 6h, 80-85%

The starting material for our synthesis was acrolein (1). Addition of nitrous acid, generated *in situ*, to the double bond of 1 gave a 54-58% yield of 3-nitropropanal (2).[5] The nitroaldehyde was then diluted with benzene and treated with methyl (triphenylphosphoranylidene)acetate to afford methyl 5-nitro-2-pentenoate (3) in 80-85% yield with a 92:8 preference for the *E* double bond isomer. In this final step, it proved important to dilute the 3-nitropropanal prior to addition of the ylide. Failure to follow this protocol resulted in partial decomposition of the aldehyde and a reduced yield of the ester product.

The current synthesis represents a considerable improvement over the original preparation and makes multigram quantities of 3 (and other ester derivatives) easily accessible. Our synthesis appears to be novel in using the Wittig reaction on an aliphatic nitro compound. Potential side reactions such as elimination and anion exchange were not observed, presumably as a result of using the relatively non-basic stabilized ylide.

Experimental

General Considerations. Acrolein (Aldrich, 97%) was dried ($CaSO_4$) and distilled (bp 53°C) prior to use, sodium nitrite (Fisher, 99.7%) was used as received and methyl (triphenylphosphoranylidene)acetate was prepared and recrystallized[6] according to literature procedures. THF was purified by distillation from $LiAlH_4$ and benzene was used as received. Glassware was dried prior to use and reactions were run under an atmosphere of dry oxygen-free nitrogen. Flash vacuum chromatography[7] was performed on silica gel (Grace, grade 62, 60-200 mesh). Gas chromatographic analyses were carried out using a Varian 3400 with an SE-30 column (6.0 m x 0.25 mm I.D, 0.25 μ film thickness) programmed between 40-200°C. IR spectra were obtained using a PE-681 instrument and are referenced to polystyrene. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 MHz and 75 MHz, respectively, using a Varian XL-300 superconducting FT instrument; chemical shifts are reported in δ units relative to internal tetramethyl-

silane. HRMS data were obtained at 70eV using a VG ZAB-2SE instrument. Elemental analyses (±0.4%) were performed by Galbraith Laboratories, Knoxville, TN.

3-Nitropropanal (2). A modification of the previously published procedure[5] was used. A 250-mL three-necked round-bottomed flask equipped with mechanical stirring, an addition funnel and a condenser (N_2 inlet) was charged with 5.60 g (6.68 mL, 0.100 mol) of acrolein, 8.63 g (0.125 mol) of sodium nitrite and 40 mL of dry THF, then cooled to 0°C. To the vigorously stirred suspension at 0°C was added 7.50 g (7.15 mL, 0.125 mol) of glacial acetic acid dropwise during 30 min. Stirring at 0°C was continued for 3 h at which time 20 mL of distilled water was added to the yellow mixture to dissolve the remaining salts. The organic phase was removed and the aqueous layer was washed with ethyl acetate (4 x 30 mL). The combined organic layers were washed with saturated sodium bicarbonate (2 x 30 mL), water (1 x 30 mL) and sodium chloride (2 x 30 mL), dried by filtration through a plug of anhydrous $MgSO_4$ and concentrated under vacuum (below 40°C) to give 5.97 g (58.0 mmol, 58.0%) of a yellow oil which proved to be pure 3-nitropropanal (NMR, GC). The compound was generally used without further purification but an analytical sample could be obtained by vacuum short path distillation. The physical and spectral data were: bp 58-60°C (0.05 mmHg), lit.[5] bp 60°C (0.05 mmHg); IR (thin film): 2860, 2750, 1730, 1560, 1385 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.80 (s, 1 H), 4.69 (t, 2 H, J = 6.0 Hz), 3.91 (t, 2 H, J = 6.0 Hz); ^{13}C-NMR ($CDCl_3$): δ 196.9, 67.5, 39.4; HRMS, *m/e* for $C_3H_5NO_3$-NO_2: calcd, 57.0340; found, 57.0344. Anal. Calcd for $C_3H_5NO_3$: C, 34.92; H, 4.89. Found: C, 35.02; H, 4.91.

Methyl 5-(*E*)-Nitro-2-pentenoate (3). In a 500-mL one-necked round-bottomed flask equipped with an oil bath and a reflux condenser (N_2 inlet), 5.97 g (58.0 mmol) of 3-nitropropanal was dissolved in 200 mL of benzene and 19.4 g (58.0 mmol) of methyl (triphenylphosphoranylidene)acetate was added. [Note: The nitroaldehyde must be diluted with benzene prior to addition of the ylide or the aldehyde darkens and effervesces with release of nitrogen oxides.] The solution was warmed to 60°C for 6 h, then cooled and concentrated at 40°C under vacuum to afford a brown semisolid residue. The residue was transferred using a minimum of hexane to the top of a 70 mm x 60 mm plug of silica gel in a fritted glass funnel. An aspirator vacuum was applied across the frit and the product was eluted through the silica gel using *ca.* 2 L of 20% ether in hexane. Concentration of the eluted

solvent under vacuum afforded the crude product as a light yellow oil. Final purification was effected by vacuum short path distillation where 7.82 g (49.2 mmol, 84.8%) methyl (*E*)-5-nitro-2-pentenoate was collected at 91-93°C (0.07 mmHg), lit.[1] bp 85-88°C (0.05 mmHg). GC analysis indicated the product to be a 92:8 mixture of the *E*:*Z* double bond isomers. The spectral data were: IR (thin film): 1730, 1668, 1560, 1440, 1385, 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.87 (dt, 1 H, J = 15.7, 6.9 Hz), 5.95 (dt, 1 H, J = 15.7, 1.5 Hz), 4.53 (t, 2 H, J = 6.8 Hz), 3.74 (s, 3 H), 2.91 (dq, 2 H, J = 6.8, 1.5 Hz); ^{13}C-NMR ($CDCl_3$): δ 165.8, 141.4, 124.1, 73.1, 51.5, 29.2; HRMS, *m/e* for $C_6H_9NO_4$-CH_3OH: calcd, 128.0348; found, 128.0349. Anal. Calcd for $C_6H_9NO_4$: C, 45.24; H, 5.70. Found: C, 45.21; H, 5.69.

Acknowledgements. The authors thank the Oklahoma Center for the Advancement of Science and Technology (OCAST Nos. HR8-084 and HR1-035) for support of this work. J.T.P. thanks the Kerr Foundation, the Grayce B. Kerr Fund and the McCasland Foundation for sponsoring the Oklahoma Summer Scholars Program. Finally, partial support by the NSF (#DMB-8603864) and OCAST (#1506) for an upgrade of our 300 MHz NMR and NSF (#BSS-8704089) for our mass spectrometry facility is acknowledged with gratitude.

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(Received in US 2 August, 1991)