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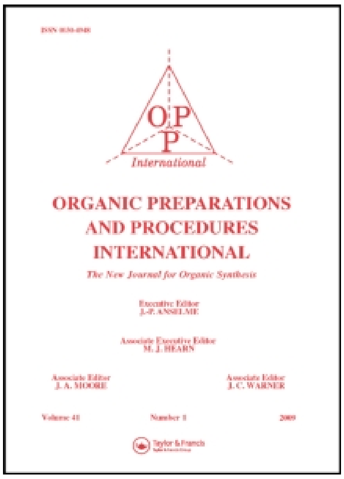

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MICHAEL REACTION OF NITROMETHANE WITH β,β-DISUBSTITUTED ACRYLATE ESTERS

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(1/15/87)

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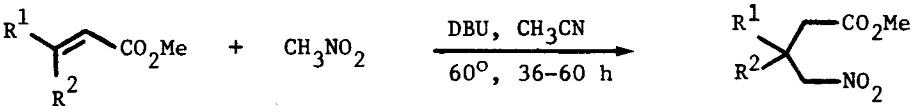
The Michael addition of nitro compounds to α,β-unsaturated esters is synthetically important due to the versatility of the nitro function in subsequent transformations.[1] Several groups[2,3] have reported the conjugate addition of nitroalkanes to α,β-unsaturated systems but, to date, only one[2] has described this reaction with a β,β-disubstituted acrylate derivative. In this singular instance, nitromethane was reacted with methyl β,β-dimethylacrylate in the presence of tetramethylguanidine to afford a 42% yield of methyl 3,3-dimethyl-4-nitrobutanoate (2a). We have improved this yield to 83% using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base and report here a general methodology for the addition of nitromethane to hindered α,β-unsaturated esters.



1a	$R^1 = R^2 = CH_3$	2a	83%
1b	$R^1,R^2 = -(CH_2)_4-$	2b	55%
1c	$R^1,R^2 = -(CH_2)_5-$	2c	74%
1d	$R^1,R^2 = -(CH_2)_6-$	2d	60%

Our results on the addition of nitromethane to hindered substrates are summarized in the Scheme. The reaction is best performed by treating one equivalent of the ester with five equivalents of nitromethane in the presence of one equivalent of DBU using acetonitrile as the solvent. Unlike the less substituted examples reported earlier, hindered reactions require heating at 60° to assure a reasonable reaction rate. Reactions were generally run on a 20-mmol scale but the preparation of 2a was carried out on a 100-mmol scale with no significant reduction in yield.

It was observed that methyl β,β-dimethylacrylate (1a) reacted with greater facility than did the cyclic compounds. Interestingly, Michael addition to the methyl cycloalkylideneacetates (1b-1d) parallels the reactivity seen in nucleophilic additions to the cyclic ketone analogs[4] with the cyclohexylidene derivative reacting more readily than the five- or seven-ring substrates. This is rationalized in terms of changes in torsional strain as one converts the sp^2 ring carbon to an sp^3 center. In 2c, addition leads to a completely staggered arrangement of bonds in the cyclohexyl ring, while a similar transformation in the five-ring system, 2b, leads to additional strain as the number of eclipsing interactions increases. Finally, the reduced reactivity of 2d probably derives from the greater steric hindrance in the seven-ring framework.

The present methodology represents a substantial improvement in the preparation of 2a and is the first report detailing the preparation of 2b-2d.

EXPERIMENTAL SECTION

Acetonitrile was dried by distillation from CaH_2 and stored over 4A molecular sieves. Nitromethane, bp. 100-101°, was distilled prior to use. Methyl β,β-dimethylacrylate[5] and the cycloalkylideneacetates[6] were prepared and purified by literature methods. IR spectra were determined using a PE-681 instrument and are referenced to polystryrene. ^{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 tetramethylsilane. High resolution mass spectra were obtained at 70 eV using a CEC 21-110B double focusing mass spectrometer. Microanalytical determinations were performed by Galbraith Laboratories, Knoxville, TN.

General Procedure for Michael Addition of Nitromethane to Hindered Acrylate Esters.- To a 10-ml acetonitrile solution of 20 mmol of the acrylate ester and 100 mmol (6.10 g, 5.40 ml) of nitromethane was added 20 mmol (3.05 g, 3.00 ml) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The mixture was stirred and heated at 60° under N_2 atmosphere until TLC and IR (C=C double bond region) indicated that starting material was consumed (36-60 hrs). The dark brown reaction mixture was poured into 1 N HCl and extracted with ether (2 X 50 ml). The combined ethereal layers were washed with water and saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated at 50° by rotary evaporation. Kugelrohr distillation under vacuum afforded a small (< 0.5 g) fraction of unreacted acrylate ester followed by the pure nitro ester as a clear to light green oil. The physical and spectral properties were as follows.

Methyl β,β-Dimethyl-4-nitrobutanoate (2a): 2.90 g (16.6 mmol, 83%); bp. 70-75° (0.5 mm Hg), lit.[2] bp. 88-90° (2 mm Hg); IR (thin film): 1740, 1552, 1378, 1230, 1190 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 4.56 (s, 2H), 3.70 (s, 3H), 2.48 (s, 2H), 1.18 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 171.4, 83.8, 51.5, 42.7, 34.2, 25.5; MS: exact mass calcd for $C_7H_{13}NO_4$-CH_3O m/z 144.0661, found m/z 144.0645.

1-[(Methoxycarbonyl)methyl]-1-nitromethylcyclopentane (2b): 2.20 g (10.9 mmol, 55%); bp. 88-94° (0.5 mm Hg); IR (thin film): 1740, 1553, 1380, 1195, 1175 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 4.71 (s, 2H), 3.72 (s, 3H), 2.61 (s, 2H), 1.71 (m, 8H); ^{13}C-NMR ($CDCl_3$): δ 171.9, 81.2, 51.5, 44.7, 40.2, 36.2, 24.0; MS: exact mass calcd for $C_9H_{15}NO_4$-CH_3O m/z 170.0817, found m/z 170.0809.

Anal. Calcd. for $C_9H_{15}NO_4$: C, 53.73; H, 7.46; N, 6.96

Found: C, 53.91; H, 7.62; N, 7.00

1-[(Methoxycarbonyl)methyl]-1-nitromethylcyclohexane (2c): 3.17 g (14.3 mmol, 74%); bp. 99-104° (0.5 mm Hg); IR (thin film): 1739, 1550, 1380, 1205, 1175 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.76 (s, 2H), 3.73 (s, 3H), 2.59 (s, 2H), 1.55 (m, 10H); ^{13}C-NMR ($CDCl_3$): δ 171.6, 81.2, 51.5 38.9, 36.9, 33.5, 25.5, 21.2; MS: exact mass calcd for $C_{10}H_{17}NO_4$-CH_3O m/z 184.0974, found m/z 184.0967.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.81; H, 7.90; N, 6.51

Found: C, 55.64; H, 8.05; N, 6.69

1-[(Methoxycarbonyl)methyl]-1-nitromethylcycloheptane (2d): 2.73 g (11.9 mmol, 60%); bp. 115-120° (0.5 mm Hg); IR (thin film): 1740, 1550, 1378, 1200, 1173 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.68 (s, 2H), 3.72 (s, 3H), 2.57 (s, 2H), 1.57 (m, 12H); ^{13}C-NMR ($CDCl_3$): δ 171.7, 81.8, 51.5, 40.6, 39.9, 35.9, 30.5, 22.3; MS: exact mass calcd for $C_{11}H_{19}NO_4$-CH_3O m/z 198.1130, found m/z 198.1135.

Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.64; H, 8.30; N. 6.11

Found: C, 57.82; H, 8.55; N. 6.05

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