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Nitroalkenes as electrophiles in the asymmetric Michael reaction involving chiral imines/enamino esters

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Abstract

Addition of 2-nitropropene to the chiral imine derived from 2-methylcyclopentanone and (*S*)-1-phenylethylamine furnished the expected Michael adduct. The latter compound was then efficiently converted into (*R*)-pentalenone through a Nef reaction. Condensation of the enamino ester derived from 2-carbethoxycyclopentanone and (*S*)-1-phenylethylamine with 1-nitropropene gave with excellent diastereo- and enantioselectivity the corresponding Michael adduct.

1. Introduction

The use of nitroalkenes as Michael acceptors has received much resurgent attention, due to the continuous discovery of efficient methods for converting aliphatic nitro groups into amines, carbonyl groups, etc.[1] Among the asymmetric versions of this reaction, condensation of chiral enamines with nitroalkenes was proved to be of great value.[2] As part of systematic studies devoted to the asymmetric Michael reaction, we recently disclosed that the conjugate addition of enamino ester (*S*)-**1** to nitroethylene **2** furnished, after hydrolytic work up, adduct (*S*)-**3** with an 80% yield and an excellent stereoselectivity (90% ee)[3] (Scheme 1). In this paper, we wish to report further investigation of this methodology, hence extending its pratical utility in asymmetric C–C bond construction.

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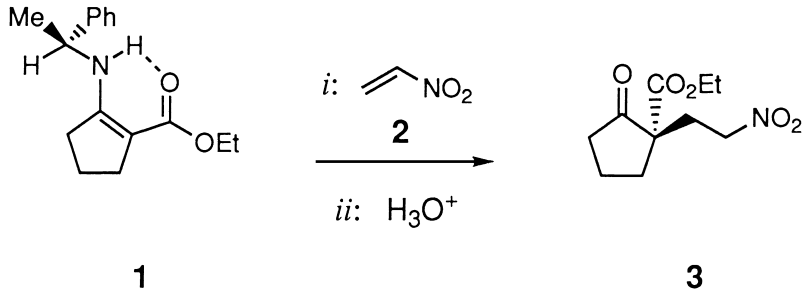
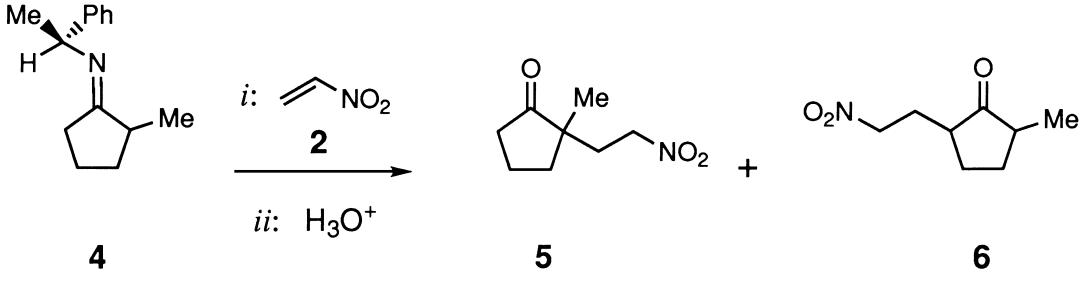


1 3

Scheme 1.

2. Results and discussion

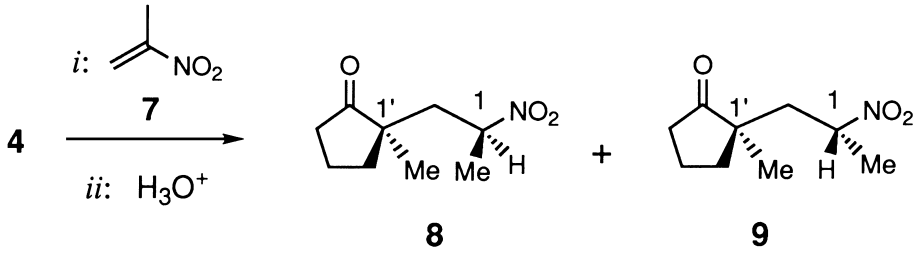
Addition of nitroethylene **2**[4] to imine (*S*)-**4**, prepared from racemic 2-methylcyclopentanone and (*S*)-1-phenylethylamine (96% ee), was examined first. This condensation (THF, 1 h at 0°C, then 20% aqueous AcOH) gave with 80% yield a nearly equimolar mixture of regioisomers **5** and **6**, as revealed by ^{1}H NMR spectroscopy. However, all attempts at chromatographic separation of the reaction mixture over silica gel failed (Scheme 2).



4 5 6

Scheme 2.

In sharp contrast, addition of imine (*S*)-**4** to the three-carbon acetonyl equivalent 2-nitropropene **7**[4] (THF, 2 h at 0°C, then 20% aqueous AcOH) was highly regioselective, furnishing with a 77% yield a mixture of diastereomeric adducts (1*S*,1′*R*)-**8** and (1*R*,1′*R*)-**9**, in a product ratio of about 9:1. The *R*-configuration at C-1′ in both isomers was determined by chemical correlation with known derivative **13**. The *S*-configuration at C-1 in major diastereomer **8**, although not definitely established, rests on the proposed transition-state model for this Michael reaction (vide infra **17**)[5] (Scheme 3).

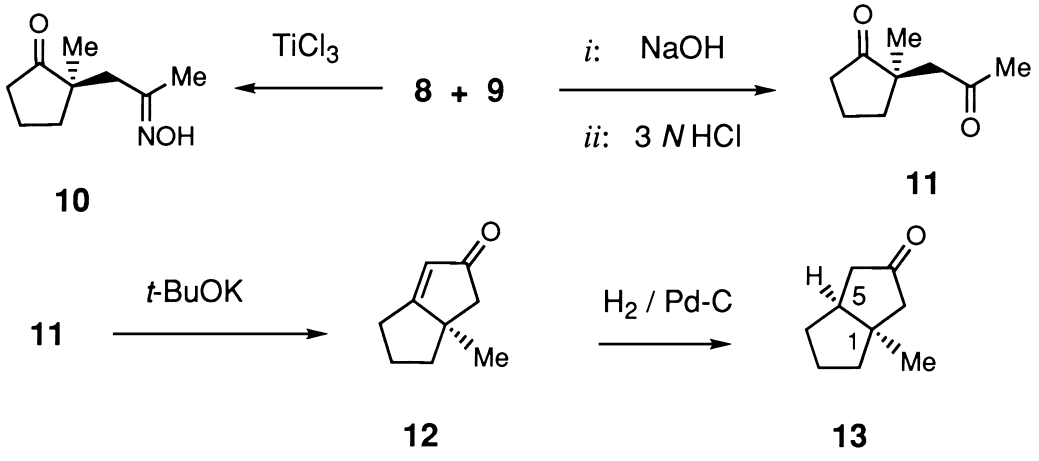


8 9

Scheme 3.

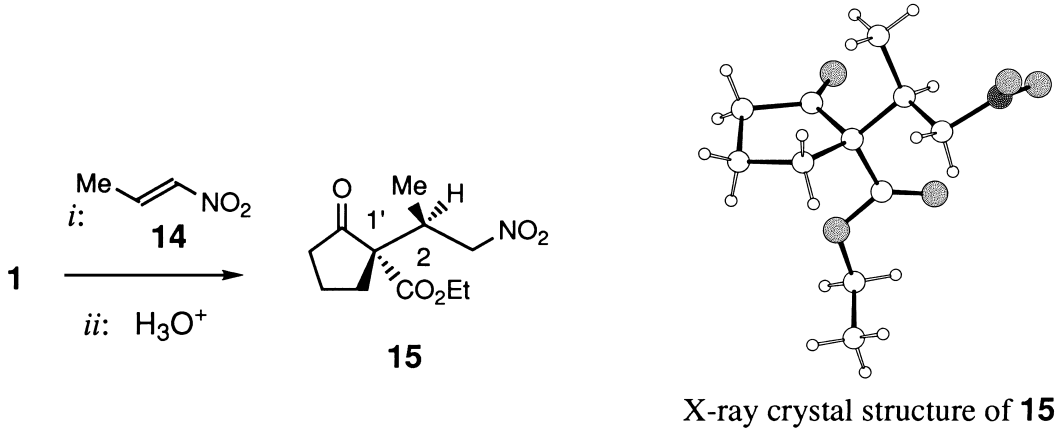
Conversion of nitro ketones **8** and **9** into corresponding diketone **11** through the Nef reaction was then studied. While treatment of the mixture of **8** and **9** with $TiCl_3$ (24 h at 20°C in H_2O) gave only oxime (*R*)-**10** in 70% yield,[6] sequential exposure of **8** and **9** to 1N NaOH in EtOH (1 h at 0°C) and 3N HCl furnished diketone (*R*)-**11** with a 68% yield.[7] The ee of **11** (=95%) was determined by ^{1}H NMR

spectroscopy, after addition of Eu(hfc)$_3$ as chiral shift reagent. The absolute configuration of compound (*R*)-**11** was unequivocally assigned by correlation with the known bicyclic ketone (1*R*,5*S*)-**13**.[8] For that purpose, **11** was first cyclized into enone (*R*)-**12** (*t*-BuOK in *t*-BuOH, 2 h at 20°C, 75% yield) which was then reduced to (1*R*,5*S*)-**13** (1 bar of H_2, Pd–C, EtOH, 95%) (Scheme 4).[9]



Scheme 4.

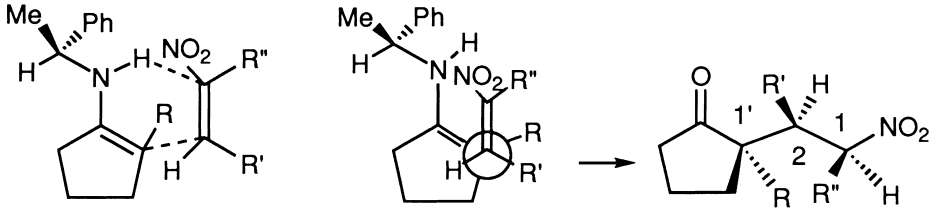
(*E*)-1-Nitropropene **14**,[4] a 1-formylethyl synthon equivalent, also constitutes a particularly attractive electrophile in the Michael reaction. While condensation of **14** with imine (*S*)-**4** afforded a complex mixture of regio- and diastereomeric adducts, addition of this nitroalkene to enamino ester (*S*)-**1** (THF, 24 h at 20°C then 20% aqueous AcOH) gave Michael adduct (1′*S*,2*S*)-**15** in 80% yield and with an excellent stereoselectivity (de and ee=95%). The structural assignment for compound **15** was verified by an X-ray diffraction analysis (Scheme 5), with the exception of the absolute configuration, founded on the proposed transition-state model **17**.



Scheme 5.

The stereochemical outcome observed in the previous experiments can be rationalized by invoking that the reaction proceeds through the cyclic ‘aza-ene-synthesis-like’ transition state **16**, which involves as nucleophilic partner enamino ester **1** (R=COOEt), or the more substituted secondary enamine in tautomeric equilibrium with imine **4** (R=Me).[5] In accordance with this mechanism, the proton borne by the nitrogen atom of the enamino ester (enamine) is transferred to the α-carbon atom of the nitroalkene, concertedly with the creation of the C–C bond. This requires a *synclinal* arrangement of the two reactants,

as shown in the corresponding compact approach **17**. According to such a model, the alkylation takes place *anti* to the bulky phenyl ring of the chiral amine moiety portrayed in its energetically preferred conformation minimizing the $A^{1,3}$-type strain (C–H bond more or less eclipsing the cyclopentene ring). This accounts for the absolute configuration in adducts **8**, **9** and **15**. On the other hand, to rationalize the stereochemical relationship of the two stereogenic centers in adducts **8** and **15**, nitroalkenes **7** and **14** need to be arranged as depicted in model **17**, namely the nitro group facing the nitrogen atom of the enamine partner (Scheme 6).



Scheme 6.

In conclusion, we have established that additions of chiral imine **4** to 2-nitropropene, and chiral enamino ester **1** to 1-nitropropene proceed smoothly, delivering the expected adducts **8** and **9**, and **15**, respectively, with a high degree of regio- and stereoselectivity. The stereochemical outcomes have been rationalized on the basis of a cyclic 'aza-ene-synthesis-like' transition state. Studies on the application of these adducts as chiral synthons for the asymmetric synthesis are underway.

3. Experimental

3.1. General

Infrared (IR) spectra were obtained on a Perkin–Elmer 841 spectrometer as neat films between NaCl plates or KBr pellets. Only the most significant absorptions are listed. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 200 P (200 MHz and 50 MHz, for ^{1}H and ^{13}C, respectively), or Bruker ARX 400 (400 MHz and 100 MHz, for ^{1}H and ^{13}C, respectively) spectrometers. Recognition of methyl, methylene, methine, and quaternary carbon nuclei in ^{13}C NMR spectra rests on the *J*-modulated spin–echo sequence. Optical rotations were measured at 20°C on a Perkin–Elmer 241 MC polarimeter in a 1 dm cell. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). Column chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM). Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which was flame-dried under a positive pressure of nitrogen. Organic layers were dried over anhydrous $MgSO_4$. Chemicals obtained from commercial suppliers were used without further purification. All elemental analyses were performed by the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin–Elmer 2400 analyzer.

3.2. (S)-α-Methyl-N-(2-methylcyclopentylidene)benzenemethanamide **4**

(*S*)-(−)-1-Phenylethylamine of 96% ee (8.9 g, 74 mmol) was added to a solution of 2-methylcyclopentanone (7.3 g, 74 mmol) and *p*-toluenesulfonic acid (0.1 g, 0.6 mmol) in toluene (60 mL). The reaction mixture was refluxed for 18 h with azeotropic removal of water. The reaction mixture was concentrated and distilled under reduced pressure to give imine **4** as a pale yellow oil (11.7 g, 79%); bp 95–98°C (0.1 torr); IR (neat, cm^{-1}) ν=1680, 1604, 1493; ^1H NMR (C_6D_6, 200 MHz) δ=1.05 and 1.20 (2 d, *J*=6.7 Hz, 3H), 1.30 and 1.40 (2 d, *J*=6.6 Hz, 3H), 1.40–2.15 (m, 7H), 4.20 (q, *J*=6.6 Hz, 1H), 6.90–7.40 (m, 5H); ^{13}C NMR (C_6D_6, 50 MHz) δ=16.8 and 16.9 (CH_3), 22.5 and 22.6 (CH_2), 25.4 and 25.5 (CH_3), 28.1 (CH_2), 32.9 and 33.0 (CH_2), 41.3 and 41.6 (CH), 61.6 and 61.9 (CH), 126.3–127.7 (5 CH), 146.7 and 147.0 (C), 178.6.

3.3. (1S,1′R)-2-Methyl-2-(2-nitropropyl)cyclopentanone **8** and (1S,1′S)-2-methyl-2-(2-nitropropyl)-cyclopentanone **9**

To an ice-cooled solution of freshly distilled imine **4** (2.93 g, 14.6 mmol) in THF (6 mL) was added dropwise 2-nitropropene **7** (1.27 g, 14.6 mmol). The reaction mixture was stirred at 0°C for 2 h and 20% aqueous acetic acid (10 mL) in methanol (6 mL) was added. After being stirred at 20°C for 2 h, the reaction mixture was concentrated in vacuo and the residue extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated under reduced pressure. Chromatographic purification on silica gel (cyclohexane:ethyl acetate, 4:1) afforded 2.08 g (77%) of a mixture of nitroketone **8** and **9** in a 9:1 ratio, as a colorless oil; IR (neat, cm^{-1}) ν=1738, 1550, 1459; ^1H NMR ($CDCl_3$, 200 MHz, only the major isomer is described) δ=0.89 (s, 3H), 1.41 (d, *J*=6.7 Hz, 3H), 1.60 (dd, *J*=15.8, 4.0 Hz, 1H), 1.65–1.90 (m, 5H), 2.05–2.24 (m, 1H), 2.30 (dd, *J*=15.8, 8.4 Hz, 1H), 4.49 (ddq, *J*=8.4, 4.0, 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz, only the major isomer is described) δ=18.2 (CH_2), 21.5 (CH_3), 21.8 (CH_3), 35.3 (CH_2), 36.8 (CH_2), 40.7 (CH_2), 47.3 (C), 80.4 (CH), 221.0 (CO).

3.4. (R)-2-Methyl-2-(oxopropyl)cyclopentanone **11**

To an ice-cooled solution of sodium hydroxide (650 mg, 16.2 mmol) in absolute ethanol (13 mL) was added 1.0 g of nitro ketones **8** and **9** (5.4 mmol). The reaction mixture was stirred at 0°C for 30 min and poured into chilled 3N HCl (30 mL). The reaction mixture was stirred at 20°C for 12 h and concentrated under reduced pressure. The oily residue was extracted with diethyl ether and the combined organic layers were successively washed with aqueous sodium bicarbonate and brine. The organic phase was dried and concentrated under reduced pressure. Chromatographic purification on silica gel (cyclohexane:ethyl acetate, 2:1) gave 566 mg (68%) of diketone **11** as a colorless oil; $[\alpha]_D^{20}$=−15.8 (*c* 3.6, EtOH); IR (neat, cm^{-1}) ν=1740, 1716; ^1H NMR ($CDCl_3$, 200 MHz) δ=0.98 (s, 3H), 1.60–2.10 (m, 4H), 2.07 (s, 3H), 2.15–2.60 (m, 2H), 2.67 (d, *J*=18.2 Hz, 1H), 2.83 (d, *J*=18.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=18.7, 22.7, 30.1, 34.6, 37.0, 45.6, 51.0, 206.4, 221.0.

3.5. (R)-5-Methyl-bicyclo[3,3,0]octen-3-one **12**

To a solution of potassium *tert*-butoxide (262 mg, 2.1 mmol) in *tert*-butanol (10 mL) was added dropwise a solution of diketone **11** (294 mg, 1.9 mmol) in *tert*-butanol (3 mL). After being stirred at 20°C for 2 h, a saturated aqueous solution of NH_4Cl was added. The mixture was extracted with CH_2Cl_2; the organic phase was dried and concentrated under reduced pressure. Chromatographic purification over

silica gel (cyclohexane:ethyl acetate, 2:1) gave 195 mg of enone **12** (75%) as a colorless oil; bp 80°C (1 torr); $[\alpha]_D^{20}$=+72.1 (*c* 6.3, EtOH); IR (neat, cm^{-1}) ν=1713, 1629; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.24 (s, 3H), 1.45 (t, *J*=10.9 Hz, 1H), 1.80–2.20 (m, 3H), 2.25 (d, *J*=17.0 Hz, 1H), 2.47 (d, *J*=17.0 Hz, 1H), 2.40–2.70 (m, 2H), 5.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=23.1 (CH_2), 24.7 (CH_2), 25.1 (CH_3), 36.4 (CH_2), 50.2 (C), 51.0 (CH_2), 123.4 (CH), 194.7 (C), 210.7 (CO).

*3.6. (1*R,*5*S*)-5-Methyl-bicyclo[3,3,0]octan-3-one **13***

A mixture of enone **12** (175 mg, 1.3 mmol) and 10% palladium on carbon (50 mg) in ethanol (5 mL) was stirred under hydrogen (4 bars) for 12 h. The mixture was filtered off and concentrated in vacuo. Distillation of the residue left enone **13** (165 mg, 95%) as a colorless oil; bp 100°C (20 torr); $[\alpha]_D$=−22.4 (*c* 0.6, $CHCl_3$); IR (neat, cm^{-1}) ν=1731, 1451; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.16 (s, 3H), 1.42 (m, 1H), 1.36–1.80 (m, 5H), 1.92–2.30 (m, 4H), 2.53 (ddd, *J*=18.0, 8.5, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=24.4 (CH_3), 27.5 (CH_2), 32.9 (CH_2), 40.0 (CH_2), 45.0 (CH_2), 46.9 (CH), 47.0 (C), 51.7 (CH_2), 220.3 (CO).

*3.7. (1*S,*2′*S*)-1-[(1-Methyl-2-nitro)ethyl]-2-oxo-cyclopentanecarboxylic acid ethyl ester **15***

(*E*)-1-Nitropropene (0.9 g, 12 mmol) was added dropwise to a solution of enamino ester **1** (1.0 g, 3.9 mmol) in THF (10 mL). The reaction mixture was stirred for 16 h at 20°C, and an additional portion of nitropropene (0.30 g, 3 mmol) was added and the stirring continued for 5 h. A solution of 20% aqueous acetic acid (20 mL) in methanol (10 mL) was added. After being stirred at 20°C for 12 h, the reaction mixture was concentrated in vacuo and the residue extracted with diethyl ether. The combined organic layers were washed with brine, dried and concentrated under reduced pressure. Chromatographic purification on silica gel (cyclohexane:ethyl acetate, 4:1) gave nitro ester **15** (750 mg, 80%) as colorless crystals; mp 53–54°C (*i*-PrOH); $[\alpha]_D^{20}$=+21.4 (*c* 2.9, EtOH); IR (neat, cm^{-1}) ν=1755, 1729, 1553; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.04 (d, *J*=6.9 Hz, 3H), 1.26 (t, *J*=7.1 Hz, 3H), 1.85–2.60 (m, 6H), 2.98 (m, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 4.26 (dd, *J*=12.8, 9.8 Hz, 1H), 4.86 (dd, *J*=12.8, 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ=13.7 (CH_3), 13.8 (CH_3), 19.3 (CH_2), 30.5 (CH_2), 35.5 (CH), 38.0 (CH_2), 61.8 (CH_2), 67.9 (C), 78.0 (CH), 168.2 (CO), 212.0 (CO); anal. calcd: C, 54.30; H, 7.05; N, 5.76; found: C, 54.25; H, 7.07; N, 5.73. Crystal data: $C_{11}H_{17}NO_5$; M_W=243.26, crystal of 0.50×0.35×0.25 mm, monoclinic, space group P 21, *Z*=2, *a*=6.407 (2), *b*=10.707 (4), *c*=9.930 (2) Å, β=106.94 (3)°, *V*=651.6 (3) $Å^3$, d_{calc}=1.24 g cm^{-3}, *F*(000)=260, λ=0.71070 Å (Mo Kα) Å, μ=0.098 mm^{-1}. Nonius CAD4 diffractometer, theta range: 2.14–27.94, 3462 collected reflexions, 3119 unique (R_{int}=0.094), 2469 observed (I=2σ(I)). The structure was refined by full-matrix least-squares with SHELX93, *R*=0.0437 for 2469 observed reflexions and wR_2=0.1273 for 3119 unique reflexions, goodness of fit=1.046. Residual electron density between −0.123 and 0.167 e $Å^{-3}$.

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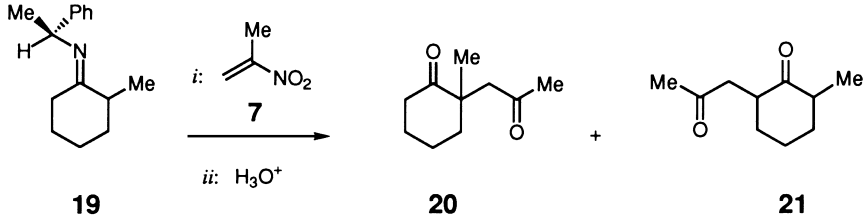
9. It should be pointed out, that in sharp contrast with the five-membered ring series, addition of imine **19** to 2-nitropropene **7** unexpectedly furnished a mixture of diketones **20** and **21** in the 6:1 ratio, in 35% yield.



19 **20** **21**