Ester- and Ketone-Substituted (±)-1-Alkyl-6-nitro-1,2,3,4-tetrahydroquinolines by a Tandem S_NAr-Michael Reaction

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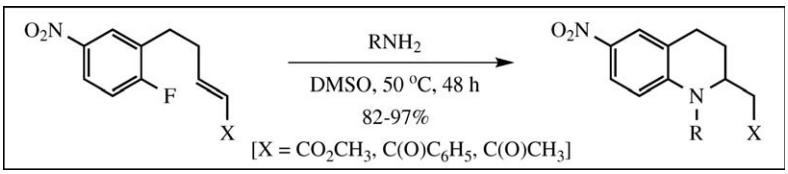

A synthesis of ester- and ketone-substituted (±)-1-alkyl-6-nitro-1,2,3,4-tetrahydroquinolines has been developed from 2-pentenoates and 2-penten-1-ones substituted at C5 by a 2-fluoro-5-nitrophenyl group. The cyclization involves an S_NAr reaction followed by a Michael addition that occurs *exo* to the final ring. A previously reported version of this annulation proceeded by an initial *endo* Michael addition (acceptor became part of the final ring) followed by an S_NAr ring closure. The current reactions proceed in 82–97% yields in DMSO using primary amines that are unbranched at the α carbon. The synthesis of the reaction substrates as well as process optimization, mechanistic studies to elucidate the reaction chronology and comparisons with the *endo* Michael variant are presented.

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INTRODUCTION

We recently described the use of a tandem Michael-S_NAr reaction sequence for the preparation of 1-alkyl-2,3-dihydro-1(4*H*)-quinolinones [2]. In that initial report, the Michael reaction occurred *via* an *endo* pathway such that the acceptor moiety became part of the final ring [3]. In the current project, we have employed a similar process to prepare ester- and ketone-substituted (±)-1-alkyl-6-nitro-1,2,3,4-tetrahydroquinolines [4,5], but the Michael reaction occurs *exo* to the final ring. These strategies offer efficient and potentially valuable routes to new members of this important family of heterocycles.

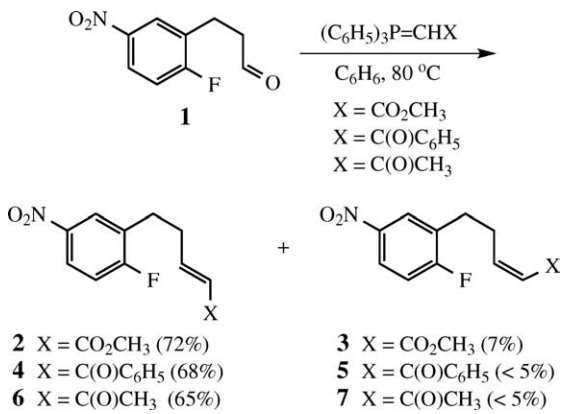
Tetrahydroquinolines are widely distributed in nature [6] and comprise the core structure in numerous pharmaceutical agents [7,8]. Specifically, tetrahydroquinoline-2-acetic esters have been used in the synthesis of 9-azasteroid antimycotic agents [7a], pyrrolobenzodiazepine antitumor antibiotics [7b], and quinoxalinediones for limiting neuronal damage in stroke and heart attack victims [8]. Efficient access to new tetrahydroquinoline derivatives bearing alternative substitution patterns could potentially yield new drugs with improved bioactivities.

RESULTS AND DISCUSSION

The synthesis of our cyclization substrates is shown in Scheme 1. Treatment of 3-(2-fluoro-5-nitrophenyl)propanal (**1**) [5e,f] with (carbomethoxymethylene)triphenylphosphorane in benzene at reflux for 12 h gave methyl (*E*)-5-(2-fluoro-5-nitrophenyl)-2-pentenoate (**2**) in 72% yield and its double bond isomer **3** in 7% yield following purification. The unsaturated ketones **4** and **6** were formed in 68 and 65% yields, respectively, almost exclusively as the *E* isomers by reacting **1** with (benzoylmethylene)triphenylphosphorane and (acetylmethylene)-triphenylphosphorane.

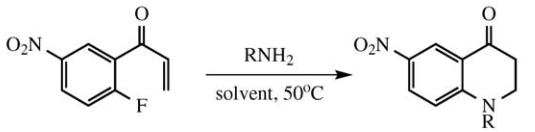
Our cyclization study sought to demonstrate the feasibility of preparing 1-alkyl-6-nitro-1,2,3,4-tetrahydroquinolines from substrates **2**, **4**, and **6** and primary amines by a tandem sequence involving the Michael and S_NAr reactions. In contrast to our earlier report [2], where Michael addition occurred to an acceptor that became

Scheme 1. Synthesis of the cyclization substrates.

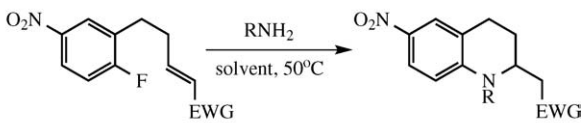


Scheme 2. Endo and Exo cyclization.

A. *Endo*: Michael acceptor becomes part of the developing ring [2]



B. *Exo*: Michael acceptor remains outside of ring



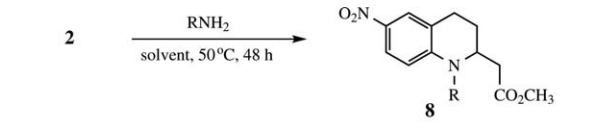
EWG = electron withdrawing group

part of the final ring (*endo* addition), the current reaction requires addition to an acceptor that remains *exo* to the ring [3] (Scheme 2). The success of this process would dramatically expand the scope of this annulation method.

We began our study by reacting unsaturated ester **2** with a series of primary amines in *N*,*N*-dimethylformamide (DMF) at 50°C. This protocol had proven successful in earlier reactions of this type. The reaction proceeded in reasonable yields of 64–81%, but the product was always accompanied by 5–10% of recovered starting material along with 2–4% of a product resulting from amine exchange with the solvent [9] and substitution of dimethylamine on the activated aromatic ring. In most cases, this substitution product was readily removed by preparative thin layer chromatography, but we sought a method that would provide the tetrahydroquinoline without this contaminant. Further experimentation showed that dimethyl sulfoxide (DMSO) was a superior solvent for this reaction and gave higher yields of the heterocycle without the dimethylamine substitution product [10].

The reaction is run by dissolving 1.00 eq of the ketone in DMSO, then adding 1.25 eq of the amine and stirring at 50°C for 48 h. Optimum yields are obtained when one additional 0.10-eq portion of the amine is added to the reaction after the first 24 h. The amine must be primary since it must react at two sites within the molecule. A major limitation of the current process is its sensitivity to steric hindrance near the nitrogen. Amines with branching at the α carbon gave tetrahydroquinolines in lower yields along with numerous other products [11]. Higher temperatures and longer reaction times in these cases yielded complex mixtures that could not be separated.

The results of our current study with ester **2** are summarized in Figure 1 and show the comparison of yields obtained in DMF and DMSO. Reaction of **2** with unbranched primary amines gave the target tetrahydroquinolines **8a-d** in 64–81% yields in DMF and in 82–93% yield in DMSO. Using the optimized conditions in DMSO, more hindered amines, such as cyclohexylamine, gave tetrahydroquinoline **8e** in significantly lower yield (48%), with the remainder being S_NAr product **9** (23%) and recovered **2** (5%).



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R	DMF Yield of **8** (%)[a,b]	DMSO Yield of **8** (%)[a,b]
Unbranched		
a $C_6H_5CH_2$	72	88
b $C_6H_5CH_2CH_2$	81	84
c *n*-C_6H_{13}	79	93
d $(CH_3)_2CHCH_2$	75	82
Branched		
e *c*-C_6H_{11}	11[c]	48[c]

[a]Each reaction also gave 5-10% of recovered starting material.
[b]These reactions also gave 2–4% of a product arising from amine exchange with solvent and substitution of dimethylamine on the aromatic ring.
[c]Compound **9** was also isolated.

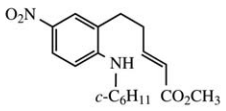

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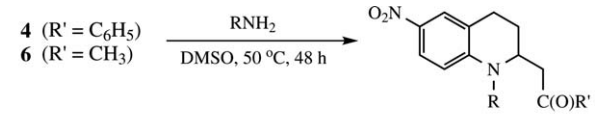
Figure 1. Cyclization of **2** and solvent study.

Further cyclization results with ketones **4** and **6** are shown in Figure 2. Using our standard protocol in DMSO solvent, the annulation with ketones proceeded somewhat better than for the ester substrate, giving the products in 88–97% yield. Again, the yields dropped precipitously when the amine was branched at the α carbon.



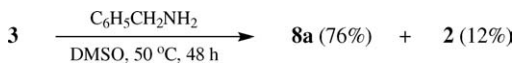
10 (R' = C_6H_5)
11 (R' = CH_3)

R	R' = C_6H_5 Yield of **10** (%)	R' = CH_3 Yield of **11** (%)
Unbranched		
a $C_6H_5CH_2$	94	93
b $C_6H_5CH_2CH_2$	95	96
c *n*-C_6H_{13}	97	92
d $(CH_3)_2CHCH_2$	88	93
Branched		
e *c*-C_6H_{11}	36[a]	37[a]

[a]Major product from a complex reaction mixture.

Figure 2. Cyclization of ketones **4** and **6**.

Scheme 3. Cyclization of *Z* substrate **3**.

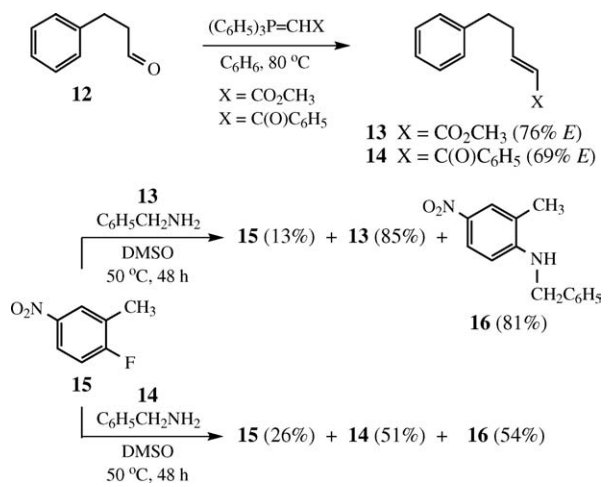


Finally, in an additional experiment, reaction of benzylamine with the *Z* substrate **3** in DMSO was attempted (Scheme 3). This reaction proceeded to give tetrahydroquinoline **8a** in slightly lower yield (76%) than that isolated from the corresponding *E* substrate **2** (88%). Interestingly, the unsaturated ester recovered from this reaction (12%) proved to be **2** rather than **3**. This observation provides experimental evidence for the reversibility of the Michael addition under the reaction conditions used [12].

The isolation of the S_NAr product from the reaction of cyclohexylamine with the unsaturated ester substrates suggests that the S_NAr reaction initiates the current annulation sequence [12]. The reaction chronology is less clear in the case of the ketones. Ketones are better Michael acceptors [13], but are also susceptible to other condensative processes. Thus, cyclohexylamine gave a much more complex product mixture in reactions with these substrates and it was not possible to identify the other products.

In an effort to elucidate the reaction chronology, competitive reaction studies were carried out (Scheme 4) using unsaturated ester **13** and ketone **14**, prepared from 3-phenylpropanal (**12**). These substrates lack the aromatic substitution necessary for the S_NAr reaction [10], and thus, can only undergo a Michael addition. If these are reacted with benzylamine in the presence of 2-fluoro-5-nitrotoluene (**15**), it should be possible to observe whether the Michael addition or the S_NAr process occurs faster in compounds having reactive environments similar to those found in our annulation substrates. Thus, in separate experiments, **13** and **14** were heated at 50°C with **15** and benzylamine in DMSO for 48 h. In each case, workup resulted in isolation of the S_NAr product, *N*-benzyl-2-methyl-4-nitroaniline (**16**), with none of the Michael product detected. The mass balance in the reaction of ester **13** was high, while the more reactive ketone **14** gave a lower return of **16** and unreacted material. Thus, it seems clear that the S_NAr reaction initiates the annulation process for the ester, but the scenario is less certain for the ketone. Though we did not detect the product from conjugate addition of benzylamine to **14**, a reverse Michael reaction [13] from such an adduct followed by reaction of the free amine with **15** could deliver the observed S_NAr product **16**.

Scheme 4. Synthesis of **13** and **14** and their competitive reactions with benzylamine in the presence of **15**.



CONCLUSION

We have developed an approach to the synthesis of (±)-1-alkyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetates based on a tandem Michael-S_NAr reaction. The reaction gives high yields in many cases but is sensitive to steric hindrance, with branching at the α carbon of the amine dramatically lowering the yield. Observations from the study suggest that the S_NAr reaction initiates the annulation sequence, and this is supported by a competitive reaction study. However, because the Michael reaction is reversible, our study does not provide incontrovertible proof of this assertion. The current study broadens the scope of tandem reactions involving the S_NAr and Michael reactions to include cyclizations that involve an *exo* Michael process.

EXPERIMENTAL

All reactions were run under dry nitrogen. Anhydrous *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were purchased commercially and syringed into reactions where they were used. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed by one of the following methods: (1) flash column chromatography [14] on silica gel (grade 62, 60–200 mesh) containing UV-active phosphor (Sorbent Technologies UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20 cm × 20 cm silica gel GF plates (Analtech 02015). Band elution for all chromatographic methods was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (*J*) are given in Hz. Unless otherwise indicated, mass spectra (electron impact/direct probe) were obtained at 70 eV.

General procedure for Wittig olefination: Methyl (*E*)-5-(2-fluoro-5-nitrophenyl)-2-pentenoate (2) and methyl (*Z*)-5-(2-fluoro-5-nitrophenyl)-2-pentenoate (3). A 100 mL benzene solution of 1.00 g (5.08 mmol) of 3-(2-fluoro-5-nitrophenyl)propanal (**1**) [5e,f] and 3.35 g (10.0 mmol) of (methoxycarbonylmethylene)triphenylphosphorane was heated under reflux for 12

h, then cooled and concentrated under vacuum. Flash chromatography of the resulting material on a 30 cm × 2.5 cm column eluted with 5% ether in hexanes gave two bands: band 1, 0.09 g (7%) of **3** as a light yellow solid, mp 58–60°C; band 2, 0.92 g (72%) of **2** as a light yellow oil. The spectral data for **2** were: IR: 1714, 1655, 1521, 1350, 1244 cm^{-1}; ^1H NMR: δ 8.14 (m, 2H), 7.18 (t, 1H, J = 9.0), 6.97 (dt, 1H, J = 15.9, 6.6), 5.87 (dt, 1H, J = 15.9, 1.1), 3.73 (s, 3H), 2.90 (t, 2H, J = 7.5), 2.58 (q, 2H, J = 7.5); ^{13}C NMR: δ 166.6, 164.6 (d, J = 256.5), 146.4, 144.3, 129.4 (d, J = 18.8), 126.2 (d, J = 6.9), 124.2 (d, J = 10.3), 122.4, 116.3 (d, J = 25.2), 51.1, 31.8, 27.5. *Anal*. Calcd for $C_{12}H_{12}FNO_4$: C, 56.92; H, 4.74; N, 5.53. Found: C, 56.98; H, 4.75; N, 5.51.

The spectral data for **3** were: IR: 1722, 1649, 1527, 1348, 1245 cm^{-1}; ^1H NMR: δ 8.17 (dd, 1H, J = 6.0, 2.7), 8.12 (ddd, 1H, J = 8.8, 7.1, 2.7), 7.17 (t, 1H, J = 8.8), 6.24 (dt, 1H, J = 11.3, 7.1), 5.85 (d, 1H, J = 11.3), 3.70 (s, 3H), 3.04 (q, 2H, J = 7.7), 2.89 (t, 2H, J = 7.7); ^{13}C NMR: δ 166.4, 164.4 (d, J = 255.9), 143.7, 144.2, 129.8 (d, J = 17.8), 126.4 (d, J = 6.7), 123.9 (d, J = 10.0), 121.0, 116.1 (d, J = 25.2), 51.2, 29.7, 27.8. *Anal*. Calcd for $C_{12}H_{12}FNO_4$: C, 56.92; H, 4.74; N, 5.53. Found: C, 57.01; H, 4.77; N, 5.48.

(*E*)-5-(2-Fluoro-5-nitrophenyl)-1-phenyl-2-penten-1-one (4). This compound was prepared as above from 1.00 g (5.08 mmol) of **1** and 3.80 g (10.0 mmol) of (benzoylmethylene)triphenylphosphorane. Purification by flash chromatography of a 30 cm × 2.5 cm column eluted with 5–15% ether in hexanes afforded 1.03 g (68%) of **4** as a light yellow solid, mp 85–86°C. IR: 1670, 1623, 1528, 1350, 1244 cm^{-1}; ^1H NMR: δ 8.17 (m, 2H), 7.90 (d, 2H, J = 7.1), 7.57 (t, 1H, J = 7.1), 7.47 (t, 2H, J = 7.7), 7.19 (t, 1H, J = 8.8), 7.05 (dt, 1H, J = 15.4, 6.6), 6.92 (d, 1H, J = 15.4), 2.98 (t, 2H, J = 7.7), 2.69 (dt, 2H, J = 7.7, 6.9); ^{13}C NMR: δ 190.4, 164.6 (d, J = 256.8), 146.4, 144.2, 137.6, 132.9, 129.5 (d, J = 18.3), 128.6 128.5, 127.1, 126.3 (d, J = 6.9), 124.2 (d, J = 10.3), 116.4 (d, J = 25.2), 32.5, 27.7. *Anal*. Calcd for $C_{17}H_{14}FNO_3$: C, 68.23; H, 4.68; N, 4.68. Found: C, 68.27; H, 4.71; N, 4.61. A small amount of **5**, contaminated with **4**, was isolated, but not used.

(*E*)-6-(2-Fluoro-5-nitrophenyl)-3-hexen-2-one (6). This compound was prepared as above from 1.00 g (5.08 mmol) of **1** and 3.18 g (10.0 mmol) of (acetylmethylene)triphenylphosphorane. Purification by flash chromatography on a 30 cm × 2.5 cm column eluted with 5–10% ether in hexanes afforded 0.78 g (65%) of **6** as a light yellow oil. IR: 1675, 1630, 1528, 1351, 1248 cm^{-1}; ^1H NMR: δ 8.14 (m, 2H), 7.20 (t, 1H, J = 9.3), 6.81 (dt, 1H, J = 15.9, 7.1), 6.10 (d, 1H, J = 15.9), 2.93 (t, 2H, J = 7.7), 2.60 (q, 2H, J = 7.1), 2.26 (s, 3H); ^{13}C NMR: δ 198.1, 164.5 (d, J = 256.5), 145.0, 144.2, 132.2, 129.3 (d, J = 18.0), 126.2 (d, J = 6.9), 124.2 (d, J = 10.3), 116.3 (d, J = 25.2), 32.1, 27.5, 27.0. *Anal*. Calcd for $C_{12}H_{12}FNO_3$: C, 60.76; H, 5.06; N, 5.91. Found: C, 60.69; H, 5.04; N, 5.94. A small amount of **7**, contaminated with **6**, was isolated, but not used.

General procedure for the tandem S_NAr-Michael reaction: Methyl (±)-1-benzyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8a). To a solution of 61 mg (0.24 mmol) of **2** in 2 mL of anhydrous DMSO was added 32 mg (0.033 mL, 0.30 mmol) of benzylamine. The reaction was stirred at 50°C for 48 h; one additional 0.10 mmol portion (0.011 mL) of the amine was added to the reaction after the first 24 h. The reaction was cooled and added to 20 mL of aqueous NaCl and extracted with 20 mL of ether (3×). The combined ether layers were washed with 20 mL of aqueous NaCl (1×), dried ($MgSO_4$) and concentrated under vacuum to give a yellow oil. Preparative thin layer chromatography on a 20 cm × 20 cm plate eluted with 20% ethyl acetate in hexanes afforded two major bands: band 1, 5 mg (8%) of recovered starting material; band 2, 72 mg (88%) of **8a** as a yellow solid, mp 135–138°C. IR: 1734, 1510, 1321 cm^{-1}; ^1H NMR: δ 7.94 (s, 1H), 7.86 (d, 1H, J = 9.3), 7.38–7.23 (complex, 3H), 7.16 (d, 2H, J = 7.1), 6.40 (d, 1H, J = 9.3), 4.72 (d, 1H, J = 17.3), 4.62 (d, 1H, J = 17.3), 4.09 (apparent sextet, 1H, J = 4.2), 3.67 (s, 3H), 3.03–2.80 (complex, 2H), 2.70 (dd, 1H, J = 15.4, 4.9), 2.57 (dd, 1H, J = 15.4, 8.8), 2.06 (m, 2H); ^{13}C NMR: δ 171.3, 149.1, 137.1, 136.4, 128.9, 127.4, 126.0, 125.2, 124.3, 120.5, 110.6, 55.4, 53.8, 51.9, 37.8, 24.6, 23.1; ms: m/z 249 (M^+-C_7H_7). *Anal*. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.06; H, 5.88; N, 8.24. Found: C, 67.09; H, 5.91; N, 8.20.

For reactions run in DMF, 2 mL of dry DMF was substituted for DMSO. The yields are given in Figure 1. These reactions all gave 5–10% of recovered substrate as well as 2–4% of a product resulting from amine exchange with the solvent and substitution of dimethylamine on the aromatic ring. This product was identified by ^1H NMR, but could not be isolated in pure form.

Tandem S_NAr-Michael reaction using the *Z* substrate: Methyl (±)-1-benzyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8a). This same procedure was carried out using 50 mg (0.20 mmol) of **3** and a total of 28 mg (0.029 mL, 0.27 mmol) of benzylamine in 2 mL of anhydrous DMSO to give 52 mg (76%) of **8a** along with 6 mg (12%) of **2**. The spectral data for these two materials matched those given above.

Methyl (±)-1-(2-phenylethyl)-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8b). This compound was prepared from 61 mg (0.24 mmol) of **2** and a total of 48 mg (0.050 mL, 0.40 mmol) of phenethylamine. Purification by preparative thin layer chromatography eluted with 20% ethyl acetate in hexanes gave 71 mg (84%) of **8b** as a yellow oil. IR: 1734, 1510, 1322 cm^{-1}; ^1H NMR: δ 8.02 (dd, 1H, J = 9.3, 2.7), 7.93 (d, 1H, J = 2.2), 7.38–7.22 (complex, 3H), 7.19 (d, 2H, J = 7.2), 6.62 (d, 1H, J = 9.3), 3.80 (ddd, 1H, J = 14.8, 7.7, 4.9), 3.73 (obscured m, 1H), 3.70 (s, 3H), 3.47 (dt, 1H, J = 14.8, 8.2), 3.02–2.68 (complex, 4H), 2.55 (dd, 1H, J = 15.4, 5.5), 2.42 (dd, 1H, J = 15.4, 8.8), 1.83 (dm, 1H, J = 13.8), 1.66 (m, 1H); ^{13}C NMR: δ 171.5, 148.4, 138.2, 136.7, 128.75, 128.70, 126.8, 125.5, 124.5, 120.4, 109.5, 55.2, 51.9 (2C), 37.5, 33.0, 24.2, 22.9; ms: m/z 263 (M^+-C_7H_7). *Anal*. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.80; H, 6.21; N, 7.91. Found: C, 67.84; H, 6.24; N, 7.79.

Methyl (±)-1-hexyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8c). This compound was prepared from 61 mg (0.24 mmol) of **2** and a total of 40 mg (0.053 mL, 0.40 mmol) of hexylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 75 mg (93%) of **8c** as a yellow oil. IR: 1736, 1510, 1321 cm^{-1}; ^1H NMR: δ 7.97 (dd, 1H, J = 9.2, 2.7), 7.90 (d, 1H, J = 2.2), 6.49 (d, 1H, J = 9.2), 3.96 (m, 1H), 3.72 (s, 3H), 3.51 (ddd, 1H, J = 14.8, 8.2, 5.5), 3.20 (dt, 1H, J = 14.8, 8.2), 2.94–2.70 (complex, 2H), 2.62 (dd, 1H, J = 15.4, 4.9), 2.48 (dd, 1H, J = 15.4, 8.8), 1.98 (dm, 1H, J = 13.7), 1.87 (m, 1H), 1.62 (m, 2H), 1.33 (m, 6H), 0.90 (distorted t, 3H, J = 6.6); ^{13}C NMR: δ 171.5, 148.8, 136.3, 125.4, 124.5, 120.2, 109.5, 54.8, 51.9,

50.3, 37.5, 31.5, 26.8, 26.6, 24.4, 22.9, 22.6, 14.0; ms: *m/z* 263 (M^+-C_5H_{11}). *Anal*. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.67; H, 7.78; N, 8.38. Found: C, 64.78; H, 7.82; N, 8.29.

Methyl (±)-1-isobutyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8d). This compound was prepared from 61 mg (0.24 mmol) of **2** and a total of 29 mg (0.040 mL, 0.40 mmol) of hexylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 60 mg (82%) of **8d** as a yellow oil. IR: 1735, 1510, 1321 cm^{-1}; ^1H NMR δ 7.95 (dd, 1H, J = 9.3, 2.7), 7.92 (s, 1H), 6.48 (d, 1H, J = 9.3), 3.96 (apparent sextet, 1H, J = 4.4), 3.72 (s, 3H), 3.50 (dd, 1H, J = 14.3, 4.9), 3.00–2.75 (complex, 3H), 2.58 (dd, 1H, J = 15.4, 5.5), 2.45 (dd, 1H, J = 15.4, 8.8), 2.12 (m, 1H), 1.99 (m, 2H), 0.97 (d, 3H, J = 6.6), 0.95 (d, 3H, J = 6.6); ^{13}C NMR δ 171.6, 149.0, 136.5, 125.6, 124.2, 119.9, 110.0, 57.8, 55.7, 52.0, 36.6, 26.6, 24.0, 22.7, 20.1; ms: *m/z* 263 (M^+-C_3H_7). *Anal*. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.75; H, 7.19; N, 9.15. Found: C, 62.84; H, 7.22; N, 9.09.

Methyl (±)-1-cyclohexyl-6-nitro-1,2,3,4-tetrahydroquinoline-2-acetate (8e). This compound was prepared from 61 mg (0.24 mmol) of **2** and a total of 39 mg (0.046 mL, 0.40 mmol) of cyclohexylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 38 mg (48%) of **8e** as a yellow solid, mp 94–96°C. IR: 1734, 1510, 1321 cm^{-1}; ^1H NMR: δ 7.96 (dd, 1H, J = 9.3, 2.7), 7.93 (s, 1H), 6.68 (d, 1H, J = 9.3), 4.19 (m, 1H), 3.71 (overlapping m, 1H and s, 3H), 3.00–2.72 (complex, 3H), 2.53 (dd, 1H, J = 15.4, 9.3), 2.45 (dd, 1H, J = 15.4, 4.9), 1.95 (m, 5H), 1.74 (m, 3H), 1.58 (m, 1H), 1.40 m, 1H), 1.22 (m, 1H); ^{13}C NMR: δ 171.5, 149.5, 136.5, 126.0, 124.1, 120.8, 111.1, 59.0, 51.9, 47.5, 38.4, 31.0, 30.3, 26.1 (2C), 25.5, 24.2, 22.8; MS: *m/z* 332 (M^+). *Anal*. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.06; H, 7.23; N, 8.43. Found: C, 64.97; H, 7.19; N, 8.45.

This reaction also afforded 3 mg (5%) of recovered **2** as a light yellow oil and 18 mg (23%) of methyl (*E*)-5-(2-cyclohexylamino-5-nitrophenyl)-2-pentenoate (**9**) as a yellow oil. The spectral data for **9** were: IR: 3397, 1721, 1657, 1532, 1314 cm^{-1}; ^1H NMR: δ 8.05 (dd, 1H, J = 9.3, 2.7), 7.95 (d, 1H, J = 2.2), 7.02 (dm, 1H, J = 15.4), 6.59 (d, 1H, J = 9.3), 5.92 (d, 1H, J = 15.4), 4.21 (br d, 1H, J = 6.0), 3.74 (s, 3H), 3.43 (m, 1H), 2.59 (apparent 2s, 4H), 2.05 (m, 2H), 1.80 (m, 2H), 1.70 (m, 1H), 1.44 (m, 2H), 1.26 (m, 3H); ^{13}C NMR: δ 166.6, 149.9, 147.0, 137.2, 124.9 (2C), 122.9, 122.2, 108.8, 51.6, 51.5, 33.0, 30.3, 28.9, 25.6, 24.7; ms (30 eV): *m/z* 332 (M^+). *Anal*. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.06; H, 7.23; N, 8.43. Found: C, 65.12; H, 7.25; N, 8.37.

(±)-2-(1-Benzyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10a). This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 43 mg (0.043 mL, 0.40 mmol) of benzylamine. Purification by preparative thin layer chromatography eluted with 25% ethyl acetate in hexanes gave 87 mg (94%) of **10a** as a yellow oil. IR: 1681, 1510, 1328 cm^{-1}; ^1H NMR: δ 7.90 (m, 4H), 7.59 (t, 1H, J = 7.7), 7.46 (t, 2H, J = 7.7), 7.36-7.24 (complex, 4H), 7.18 (d, 1H, J = 7.1), 6.42 (d, 1H, J = 9.3), 4.71 (d, 1H, J = 17.0), 4.64 (d, 1H, J = 17.0), 4.38 (m, 1H), 3.28 (d, 2H, J = 6.0), 2.93 (m, 2H), 2.09 (m, 2H); ^{13}C NMR: δ 197.8, 149.4, 136.9, 136.6, 136.5, 133.6, 128.9, 128.8, 128.0, 127.4, 126.1, 125.3, 124.4, 120.4, 110.5, 54.7, 53.9, 41.5, 24.8, 23.3. ms: *m/z* 295 (M^+-C_7H_7). *Anal*. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.61; H, 5.70; N, 7.25. Found: C, 74.74; H, 5.73; N, 7.14.

(±)-2-(6-Nitro-1-phenethyl-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10b). This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 48 mg (0.050 mL, 0.40 mmol) of phenethylamine. Purification by preparative thin layer chromatography eluted with 20% ethyl acetate in hexanes gave 91 mg (95%) of **10b** as a yellow oil. IR 1681, 1510, 1327 cm^{-1}; ^1H NMR: δ 8.02 (dd, 1H, J = 9.3, 2.7), 7.94 (d, 1H, J = 2.7), 7.90 (d, 2H, J = 8.0), 7.59 (t, 1H, J = 7.7), 7.46 (t, 2H, J = 7.7), 7.36-7.21 (complex, 4H), 7.19 (d, 1H, J = 7.4), 6.61 (d, 1H, J = 9.3), 4.05 (m, 1H), 3.78 (ddd, 1H, J = 14.3, 8.2, 5.5), 3.49 (dt, 1H, J = 14.8, 8.2), 3.12 (m, 2H), 3.05–2.70 (complex, 4H), 1.87 (dm, 1H, J = 13.2), 1.72 (m, 1H); ^{13}C NMR: δ 198.0, 148.7, 138.3, 136.6, 136.5, 133.6, 128.8 (2C), 128.7, 128.0, 126.7, 125.6, 124.5, 120.4, 109.5, 54.5, 52.0, 41.5, 33.0, 24.5, 23.1; ms: *m/z* 309 (M^+-C_7H_7). *Anal*. Calcd for $C_{25}H_{24}N_2O_3$: C, 75.00; H, 6.00; N, 7.00. Found: C, 75.16; H, 6.05; N, 6.93.

(±)-2-(1-Hexyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10c). This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 40 mg (0.053 mL, 0.40 mmol) of hexylamine. Purification by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes gave 88 mg (97%) of **10c** as a yellow oil. IR: 1682, 1510, 1328 cm^{-1}; ^1H NMR: δ 7.95 (m, 4H), 7.60 (t, 1H, J = 7.7), 7.48 (t, 2H, J = 7.7), 6.49 (d, 1H, J = 8.8), 4.27 (m, 1H), 3.51 (ddd, 1H, J = 14.3, 8.8, 5.5), 3.20 (d, 2H, J = 7.1), 3.20 (obscured m, 1H), 2.84 (m, 2H), 2.03 (dm, 1H, J = 11.0), 1.91 (m, 1H), 1.62 (m, 2H), 1.32 (complex, 6H), 0.89 (distorted t, 3H, J = 6.6); ^{13}C NMR: δ 198.1, 149.1, 136.7, 136.2, 133.6, 128.8, 128.0, 125.5, 124.5, 120.0, 109.4, 54.2, 50.4, 41.3, 31.5, 26.8, 26.6, 24.6, 23.1, 22.5, 13.9; ms: *m/z* 309 (M^+-C_5H_{11}). *Anal*. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.63; H, 7.37; N, 7.37. Found: C, 72.58; H, 7.34; N, 7.39.

(±)-2-(1-Isobutyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10d). This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 29 mg (0.040 mL, 0.40 mmol) of isobutylamine. Purification by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes gave 74 mg (88%) of **10d** as a yellow oil. IR: 1681, 1510, 1324 cm^{-1}; ^1H NMR: δ 7.93 (m, 4H), 7.60 (t, 1H, J = 7.7), 7.47 (t, 2H, J = 7.7), 6.48 (d, 1H, J = 8.8), 4.25 (m, 1H), 3.47 (dd, 1H, J = 14.8, 4.9), 3.17 (d, 2H, J = 7.1), 3.00–2.75 (complex, 3H), 2.12 (m, 1H), 2.04 (m, 2H), 0.99 (d, 3H, J = 6.6), 0.94 (d, 3H, J = 6.6); ^{13}C NMR: δ 198.2, 149.3, 136.7, 136.3, 133.6, 128.8, 128.0, 125.7, 124.3, 119.8, 110.0, 57.9, 55.1, 40.4, 26.6, 24.2, 22.9, 20.1 (2C); ms: *m/z* 309 (M^+-C_3H_7). *Anal*. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.59; H, 6.82; N, 7.95. Found: C, 71.77; H, 6.85; N, 7.89.

(±)-2-(1-Cyclohexyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone (10e). This compound was prepared from 72 mg (0.24 mmol) of **4** and a total of 39 mg (0.046 mL, 0.40 mmol) of cyclohexylamine. Purification by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes gave 32 mg (36%) of **10e** as a yellow oil. IR 1679, 1503, 1324 cm^{-1}; ^1H NMR: δ 7.98 (dd, 1H, J = 9.3, 2.7), 7.93 (obscured signal, 1H), 7.92 (d, 2H, J = 7.1), 7.60 (t, 1H, J = 7.1), 7.47 (t, 2H, J = 7.7), 6.71 (d, 1H, J = 9.3), 4.50 (m, 1H), 3.74 (tt, 1H, J = 11.5, 3.3), 3.31 (dd, 1H, J = 17.6, 9.3), 2.97 (dd, 1H, J = 17.6, 3.3), 2.81 (m, 3H), 2.04 (dm, 1H, J = 13.2), 1.90 (m, 3H), 1.85–1.50 (complex, 4H), 1.39 (m, 2H), 1.20 (tt, 1H, J = 13.2, 3.3); ^{13}C NMR: δ 198.0, 149.9, 136.8,

136.4, 133.6, 128.8, 128.6, 128.5, 128.0, 126.1, 124.2, 120.6, 111.1, 59.1, 46.8, 42.1, 31.1, 30.3, 26.1 (2C), 25.4, 24.3, 23.0; ms: *m*/*z* 378 (M^+). *Anal*. Calcd for $C_{23}H_{26}N_2O_3$: C, 73.02; H, 6.88; N, 7.41. Found: C, 73.12; H, 6.92; N, 7.34. No other products could be isolated from this reaction in pure form.

(±)-1-(1-Benzyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)propan-2-one (11a). This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 43 mg (0.043 mL, 0.40 mmol) of benzylamine. Purification by preparative thin layer chromatography eluted with 20% ethyl acetate in hexanes gave 72 mg (92%) of **11a** as a yellow oil. IR: 1714, 1511, 1320 cm^{-1}; ^1H NMR: δ 7.93 (d, 1H, *J* = 2.7), 7.85 (dd, 1H, *J* = 9.3, 2.7), 7.38–7.22 (complex, 3H), 7.15 (d, 2H, *J* = 7.1), 6.40 (d, 1H, *J* = 9.3), 4.66 (d, 1H, *J* = 17.6), 4.61 (d, 1H, *J* = 17.6), 4.18 (sextet, 1H, *J* = 3.8), 2.86 (m, 2H), 2.80 (dd, 1H, *J* = 17.6, 4.9), 2.72 (dd, 1H, *J* = 17.6, 7.7), 2.13 (s, 3H), 2.00 (m, 2H); ^{13}C NMR: δ 206.2, 149.4, 136.9, 136.5, 128.9, 127.4, 126.1, 125.2, 124.4, 120.4, 110.5, 53.9, 53.8, 46.9, 30.8, 24.9, 23.3; ms: *m*/*z* 233 (M^+-C_7H_7). *Anal*. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17; N, 11.57, Found: C, 70.33; H, 6.14; N, 11.64.

(±)-1-(6-Nitro-1-phenethyl-1,2,3,4-tetrahydroquinolin-2-yl) propan-2-one (11b). This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 48 mg (0.050 mL, 0.40 mmol) of phenethylamine. Purification by preparative thin layer chromatography eluted with 15% ethyl acetate in hexanes gave 78 mg (96%) of **11b** as a yellow oil. IR: 1714, 1514, 1318 cm^{-1}; ^1H NMR: δ 8.01 (dd, 1H, *J* = 9.3, 2.7), 7.91 (d, 1H, *J* = 2.7), 7.37–7.22 (complex, 3H), 7.19 (d, 2H, *J* = 7.1), 6.60 (d, 1H, *J* = 9.3), 3.85 (m, 1H), 3.80 (ddd, 1H, *J* = 14.3, 8.8, 5.5), 3.46 (dt, 1H, *J* = 14.2, 7.7), 2.90 (m, 2H), 2.74 (m, 2H), 2.66 (dd, 1H, *J* = 17.6, 4.9), 2.58 (dd, 1H, *J* = 17.6, 7.1), 2.14 (s, 3H), 1.79 (dm, 1H, *J* = 13.2), 1.66 (m, 1H); ^{13}C NMR: δ 206.5, 148.7, 138.3, 136.4, 128.74, 128.66, 126.7, 125.5, 124.5, 120.3, 109.4, 53.5, 51.9, 46.7, 32.9, 30.9, 24.4, 23.0; ms: *m*/*z* 247 (M^+-C_7H_7). *Anal*. Calcd for $C_{20}H_{22}N_2O_3$: C, 71.01; H, 6.51; N, 8.28. Found: C, 71.09; H, 6.55; N, 8.22.

(±)-1-(1-Hexyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)propan-2-one (11c). This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 40 mg (0.053 mL, 0.40 mmol) of hexylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 70 mg (92%) of **11c** as a yellow oil. IR: 1714, 1510, 1315 cm^{-1}; ^1H NMR: δ 7.97 (dd, 1H, *J* = 9.3, 2.7), 7.90 (d, 1H, *J* = 2.7), 6.48 (d, 1H, *J* = 9.3), 4.05 (m, 1H), 3.49 (ddd, 1H, *J* = 14.8, 8.8, 5.5), 3.16 (ddd, 1H, *J* = 14.8, 8.8, 5.5), 2.78 (m, 2H), 2.68 (m, 2H), 2.19 (s, 3H), 1.90 (m, 2H), 1.59 (m, 2H), 1.41–1.23 (complex, 6H), 0.90 (distorted t, 3H, *J* = 6.6); ^{13}C NMR: δ 206.5, 149.0, 136.2, 125.5, 124.5, 120.0, 109.4, 53.3, 50.3, 46.6, 31.5, 31.0, 26.8, 26.6, 24.6, 23.1, 22.6, 14.0; ms: *m*/*z* 247 (M^+-C_5H_{11}). *Anal*. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.92; H, 8.18; N, 8.81. Found: C, 67.99; H, 8.24; N, 8.76.

(±)-1-(1-Isobutyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl)propan-2-one (11d). This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 29 mg (0.040 mL, 0.40 mmol) of isobutylamine. Purification by preparative thin layer chromatography eluted with 5% ethyl acetate in hexanes gave 65 mg (93%) of **11d** as a yellow oil. IR: 1718, 1510, 1318 cm^{-1}; ^1H NMR: δ 7.94 (dd, 1H, *J* = 9.3, 2.7), 7.91 (br s, 1H), 6.47 (d, 1H, *J* = 9.3), 4.04 (septet, 1H, *J* = 3.3), 3.47 (dd, 1H, *J* = 14.3, 4.9), 2.81 (m, 3H), 2.65 (d, 2H, *J* = 6.6), 2.18 (s, 3H), 2.10 (m, 1H), 1.95 (m, 2H), 0.97 (d, 3H, *J* = 6.6), 0.94 (d, 3H, *J* = 6.6); ^{13}C NMR: δ 206.6, 149.3, 136.3, 125.3, 124.3, 119.7, 109.9, 57.7, 54.2, 45.6, 31.0, 26.6, 24.1, 22.9, 20.1 (2C); ms: *m*/*z* 247 (M^+-C_3H_7). *Anal*. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.21; H, 7.59; N, 9.66. Found: C, 66.26; H, 7.61; N, 9.58.

(±)-1-(1-Cyclohexyl-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl) propan-2-one (11e). This compound was prepared from 57 mg (0.24 mmol) of **6** and a total of 39 mg (0.046 mL, 0.40 mmol) of cyclohexylamine. Purification by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes gave 28 mg (37%) of **11e** as a yellow solid, mp 117–120°C. IR: 1714, 1509, 1321 cm^{-1}; ^1H NMR: δ 7.96 (dd, 1H, *J* = 9.3, 2.7), 7.91 (br s, 1H), 6.67 (d, 1H, *J* = 9.3), 4.27 (m, 1H), 3.70 (tt, 1H, *J* = 11.5, 3.3), 2.84–2.67 (complex, 4H), 2.52 (dd, 1H, *J* = 7.1, 3.3), 2.16 (s, 3H), 2.01–1.81 (complex, 4H), 1.80–1.54 (complex, 4H), 1.40 (m, 2H), 1.25 (tt, 1H, *J* = 13.2, 3.3); ^{13}C NMR: δ 206.5, 149.8, 136.3, 126.0, 124.1, 120.5, 111.0, 59.0, 47.4, 46.1, 31.1, 30.3, 26.1, 25.4, 24.3, 22.9; ms: *m*/*z* 316 (M^+). *Anal*. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.35; H, 7.59; N, 8.86. Found: C, 68.44; H, 7.64; N, 8.77. No other products could be isolated from this reaction in pure form.

Methyl (*E*)-5-phenyl-2-pentenoate (13). This compound was prepared as described for **2** using 1.00 g (7.46 mmol) of **12** and 3.73 g (11.2 mmol) of (methoxycarbonylmethylene)triphenylphosphorane in benzene. Flash chromatography on a 30 cm × 2.5 cm column eluted with 5–10% ether in hexanes gave 1.07 g (76%) of **13** as a colorless oil [15]. IR: 1729, 1659 cm^{-1}; ^1H NMR: δ 7.29 (m, 2H), 7.19 (m, 3H), 7.01 (dt, 1H, *J* = 15.4, 7.1), 5.85 (dt, 1H, *J* = 15.4, 1.6), 3.72 (s, 3 H), 2.77 (t, 2H, *J* = 7.1), 2.51 (q, 2H, *J* = 7.1); ^{13}C NMR: δ 166.9, 148.3, 140.7, 128.4, 128.3, 126.1, 121.4, 51.4, 34.3, 33.9; ms (30 eV): *m*/*z* 190 (M^+). *Anal*. Calcd for $C_{12}H_{14}O_2$: C, 75.79; H, 7.37. Found: C, 75.90; H, 7.41.

(*E*)-1,5-Diphenyl-2-penten-1-one (14). This compound was prepared as described for **2a** from 1.00 g (7.46 mmol) of **12** and (11.2 mmol) of (benzoylmethylene)triphenylphosphorane. Flash chromatography on a 30 cm × 2.5 cm column eluted with 8–12% ether in hexanes gave 1.21 g (69%) of **14** as a yellow oil [15]. IR 1670, 1623 cm^{-1}; ^1H NMR: δ 7.87 (d, 2H, *J* = 7.4), 7.54 (t, 1H, *J* = 7.4), 7.44 (t, 2H, *J* = 7.4), 7.30 (t, 2H, *J* = 7.4), 7.22 (m, 3H), 7.08 (dt, 1H, *J* = 15.4, 7.1), 6.86 (d, 1H, *J* = 15.4), 2.85 (t, 2H, *J* = 7.1), 2.64 (q, 2H, *J* = 7.1); ^{13}C NMR: δ 190.8, 148.4, 140.7, 137.8, 132.6, 128.5, 128.4 (2C), 128.3, 126.5, 126.1, 34.47, 34.44; ms (30 eV): *m*/*z* 236 (M^+). *Anal*. Calcd for $C_{17}H_{16}O$: C, 86.44; H, 6.78. Found: C, 86.37; H, 6.74.

Control experiment: Competitive reaction of benzylamine with 13 and 15. A mixture of 95 mg (0.50 mmol) of **13**, 75 mg (0.50 mmol) of **15** and 54 mg (0.055 mL, 0.50 mmol) of benzylamine in 3 mL of anhydrous DMSO was heated at 50°C for 48 h. The mixture was cooled, worked up with aqueous NaCl and purified by preparative thin layer chromatography eluted with 10% ethyl acetate in hexanes to give three major bands: band 1, 10 mg (13%) of recovered **15**; band 2: 81 mg (85%) of recovered **13**; band 3, 92 mg (81%) of *N*-benzyl-2-methyl-4-nitroaniline (**16**) as a yellow solid, mp 99–100°C. The spectral data for **16** were: IR: 3417, 1531, 1328 cm^{-1}; ^1H NMR: δ 8.00 (dd, 1H, *J* = 8.2, 2.2), 7.99 (s, 1H), 7.42–7.30 (complex, 5H), 6.54 (d, 1H, *J* = 8.2), 4.66 (br s, 1H), 4.48 (d, 2H, *J* = 4.9), 2.21 (s, 3H); ^{13}C NMR: δ 151.3,

137.4, 134.8, 129.0, 127.8, 127.3, 126.0, 124.6, 121.2, 108.3, 47.8, 17.3; ms: *m*/*z* 151 (M^+-C_7H_7). *Anal*. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.79; N, 11.57. Found: C, 69.45; H, 5.79; N, 11.52.

Control experiment: Competitive reaction of benzylamine with 14 and 15. A mixture of 118 mg (0.50 mmol) of **14**, 75 mg (0.50 mmol) of **15** and 54 mg (0.055 mL, 0.50 mmol) of benzylamine was reacted, worked up and purified as above to give: band 1, 20 mg (26%) of recovered **15**; band 2: 60 mg (51%) of recovered **14**; band 3, 61 mg (54%) of **16**. This reaction mixture was more complex due to the greater reactivity of the ketone, but none of the conjugate addition product was detected.

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[12] In our earlier work, which focused on unhindered substrates that close by an *endo* process, evidence suggested that the Michael addition initiated the annulation sequence (see Ref 2). Subsequent experiments, however, have shown that increased substitution on the β-carbon of the Michael acceptors results in a reversal of the steps in this reaction. The results of this study will be reported in due course.

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