Aryl-Fused Nitrogen Heterocycles by a Tandem Reduction−Michael Addition Reaction

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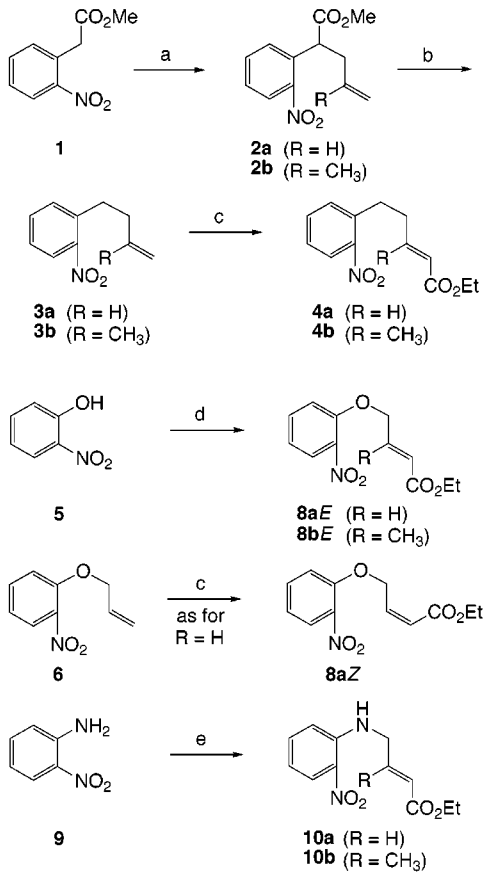
Introduction

The 1,2,3,4-tetrahydroquinoline, 3,4-dihydro-2*H*-1,4-benzoxazine, and 1,2,3,4-tetrahydroquinoxaline ring systems are important structural units in many bioactive compounds.[2−4] A review of the literature[2−4] reveals that while the parent molecules are easily prepared, substituted cases are considerably more challenging. As part of our synthetic studies, we sought to prepare derivatives of these compounds by a tandem reduction−Michael addition reaction using suitably substituted nitroarenes. Such an approach would permit the synthesis of structures bearing unique substitution patterns, including functionality that could be further elaborated in subsequent synthetic steps.

Previously reported tandem sequences involving nitroarenes include reduction−reductive amination[5] and reduction−lactam formation.[6] In these processes, the aromatic nitro group is easily reduced[7] in the presence of an aldehyde, ketone, or ester, and the resulting amine reacts with the carbonyl group in a subsequent step. When evaluating reaction conditions for a reduction-Michael procedure, the sensitivity of the acceptor moiety must be considered. The reagent must selectively reduce the nitro group in the presence of an α,β-unsaturated ester and, in the case of dihydrobenzoxazines and tetrahydroquinoxalines, be mild enough to preserve allylic ether and amine functionality. We wish to report that the use of iron powder in refluxing glacial acetic acid successfully carries out this transformation in high yield.

Scheme 1. Synthesis of Cyclization Substrates[a]



[a] Key: (a) CH_2=C(R)CH_2I, K_2CO_3, 18-crown-6, CH_3CN, 82 °C, 92%; (b) (i) NaOH, aqueous dioxane; (ii) K_2CO_3, DMF, 50 °C, 92%; (c) for R = H, (i) O_3, CH_3OH, −78 °C; (ii) $(CH_3)_2S$, HOAc, −78 °C → rt; (iii) Ph_3P=$CHCO_2Et$, PhH, 80 °C, 52−56%; for R = CH_3, (i) O_3, CH_3OH, −78 °C; (ii) $(CH_3)_2S$, *p*-TsOH, −78 °C → rt; (iii) $(MeO)_2P(O)CH_2CO_2Et$, NaH, THF−DMSO, rt, 61%; (d) $BrCH_2$-C(R)=$CHCO_2Et$ (R = H, **7a**, R = CH_3, **7b**), K_2CO_3, acetone, 0 °C, 55−58%; (e) **7a** or **7b** (0.5 equiv), 100 °C, 70−75%.

Synthesis of the Cyclization Substrates. Scheme 1 summarizes the synthesis of the cyclization substrates. Precursors for the tetrahydroquinoline systems were prepared from methyl (2-nitrophenyl)acetate (**1**)[8] by a sequence involving (a) alkylation of the activated benzylic carbon with an allylic iodide to give **2**,[9] (b) ester hydrolysis and decarboxylation to give **3**,[10] and (c) ozonolysis-Wittig[11] (or Wadsworth−Emmons)[12] conversion of the

(1) Oklahoma State University Freshman Research Scholar, 1999−2000.

(2) For recent reviews on tetrahydroquinolines, see: (a) Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem.* **1998**, *35*, 761−785. (b) Katritsky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031−15070. See also: (c) Gilchrist, T. L.; Rahman, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1203−1207. (d) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Nishimura, H.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, Y.; Nakamura, M.; Ogita, K.; Yoneda, Y. *J. Med. Chem.* **1994**, *37*, 3956−3968.

(3) For a recent review on benzoxazines, see: (a) Sainsbury, M. *Rodd's Chem. Carbon Compd.*, 2nd ed.; Elsevier: Amsterdam, 1998; pp 465−511. See also: (b) Matsuoka, H.; Ohi, N.; Mihara, M.; Suzuki, H.; Miyamoto, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Takeda, Y.; Yano, K.; Kuroki, T. *J. Med. Chem.* **1997**, *40*, 105−111.

(4) For reviews on quinoxalines, see: (a) Sakata, G.; Makino, K.; Kurasawa, Y. *Heterocycles* **1988**, *27*, 2481−2515. (b) Cheeseman, G. W. H.; Werstiuk, E. S. G. *Adv. Heterocycl. Chem.* **1978**, *22*, 367−431. See also (c) Awad, I. M. A. *J. Chem. Technol. Biotechnol.* **1992**, *53*, 227−236. (d) Kleim, J.-P.; Bender, R.; Billhardt, U.-M.; Meichsner, C.; Riess, G.; Rösner, M.; Winkler, I.; Paessens, A. *Antimicrob. Agents Chemother.* **1993**, *37*, 1659−1664. (e) Kleim, J.-P.; Rösner, M.; Winkler, I.; Paessens, A.; Kirsch, R.; Hsiou, Y.; Arnold, E.; Riess, G. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 34−38.

(5) Reduction-reductive amination: (a) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985; pp 82−93. (b) Artico, M.; DeMartino, G.; Filacchione, G. Giuliano, R. *Farmaco, Ed. Sci.* **1969**, *24*, 276−284; *Chem Abstr.* **1970**, *70*, 96775a.

(6) Reduction−lactam formation: (a) Floyd, D. M.; Moquin, R. V.; Atwal, K. S.; Ahmed, S. Z.; Spergal, S. H.; Gougoutas, J. Z.; Malley, M. F. *J. Org. Chem.* **1990**, *55*, 5572−5579. (b) Tapia, R. A.; Centella, C. R.; Valderrama, J. A. *Synth. Commun.* **1999**, *29*, 2163-2168.

(7) For a survey of most of the methods for nitroarene reduction, see Hudlicky, M. *Reductions in Organic Chemistry*, 2nd ed.; American Chemical Society: Washington D.C., 1996.

(8) The acid was esterified using MeOH/HCl (g); see: Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: New York, 1989; p 700.

(9) Makosza, M.; Tyrala, A. *Synth. Commun.* **1986**, *16*, 419−423.

(10) Bull D. J.; Fray, M. J.; Mackenny, M. C.; Malloy, K. A. *Synlett* **1996**, 647−648.

(11) Bunce, R. A.; Pierce, J. D. *Org. Prep. Proced. Int.* **1987**, *19*, 67−71.

(12) Balsevich, J. *Can. J. Chem.* **1983**, *61*, 1053−1059.

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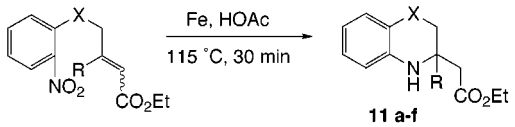
Table 1. Ring Closures by Tandem Reduction−Michael Addition



11 a-f

substrate	X	R	product	yield (%)
4a	CH_2	H	**11a**	98
4b	CH_2	CH_3	**11b**	89
8a*E*	O	H	**11c**	94
8a*Z*	O	H	**11c**	98
8b*E*	O	CH_3	**11d**	88
10a	NH	H	**11e**	89
10b	NH	CH_3	**11f**	86

side chain double bond to afford acrylate **4**. Starting materials for the dihydrobenzoxazines were prepared from 2-nitrophenol (**5**) and 2-allyloxy-1-nitrobenzene (**6**).[13,14] Direct alkylation of **5** with ethyl (*E*)-4-bromo-2-butenoate (**7a**) using K_2CO_3 in acetone at 0−20 °C afforded **8a***E*;[15,16] similar alkylation with ethyl (*E*)-4-bromo-3-methyl-2-butenoate (**7b**)[17] gave **8b***E*. Ozonolysis of **6** followed by Wittig[11] olefination produced **8a***Z*.[18] Finally, tetrahydroquinoxaline precursors **10a** and **10b** were generated by heating 2-nitroaniline (**9**) with **7a** and **7b**, respectively.[19]

Results and Discussion

The results of our tandem reduction−Michael addition synthesis of aryl-fused nitrogen heterocycles are summarized in Table 1. Treatment of 1 equiv of each substrate with 6 equiv of iron powder in glacial acetic acid at 115 °C for 30 min gave the indicated yields after purification by preparative thin-layer chromatography. Yields were uniformly high regardless of double-bond geometry or substitution at the Michael terminus.

The mechanism of the reaction involves initial reduction of the nitro group to an amine which undergoes Michael addition to the pendent acrylate by a favorable *six-exo-trig* process.[20] The use of 6 equiv (a 2-fold excess) of iron assured that the required six electrons were available for the reduction.[21] Ring closure by Michael addition proceeded rapidly under the reaction conditions, even in cases where a methyl group on the acrylate acceptor hindered cyclization.[22] Double-bond geometry also had little effect on the cyclization. It was noted, however, that the *Z* olefin reacted more rapidly and gave higher yields than the *E* isomer. This observation likely reflects the higher reactivity of the *Z* acrylate as well as the decreased steric interaction between the ester and the approaching nucleophile for the *Z* acceptor.

Earlier studies reported iron to be an extremely mild reagent that permits reduction of nitroarenes bearing halogens and carbonyl-containing groups.[7,23,24] Our results have confirmed and extended this finding. In the current reaction, iron powder was used directly in refluxing glacial acetic acid with no reduction or degradation of the side chain.

Several other reducing agents were also investigated but gave less satisfactory results.[25] The same tandem sequence occurred using 6 equiv of iron powder in water containing 0.25 equiv of $FeSO_4 \cdot 7H_2O$ at 100 °C,[26] but yields were 10−20% lower and some side chain cleavage (10−15%) was observed in the ether-containing substrates.[27] Reduction of **4a**, **8a***E* and **10a** with 6 equiv of $Na_2S_2O_4$ (sodium dithionite)[28] in aqueous ethanol containing excess $NaHCO_3$ at 60 °C gave less than 40% of the desired heterocycles along with several minor side products. Finally, hydrogenation of **8a***E* at 1 atm over 5% Pd/C in ethanol at 30 °C resulted in reduction of both the nitro group and the side chain double bond; none of the heterocyclic product was detected.

In summary, we have developed a tandem reduction−Michael addition sequence for the preparation of several types of aryl-fused nitrogen heterocycles. The procedure is simple, clean, inexpensive and efficient, providing the target ring systems in 2−5 steps. The yields for the ring closure are excellent, and the products are easily purified by chromatography. We are continuing our work to explore new synthetic approaches to heterocyclic systems.

Experimental Section

Commercial reagents and solvents were used as received. Potassium carbonate was ground to a fine powder, dried under vacuum at 120 °C for 24 h, and stored in an oven at 120 °C. Methyl (2-nitrophenyl)acetate (**1**),[8] 2-allyloxy-1-nitrobenzene (**6**),[13] and ethyl (*E*)-4-bromo-3-methyl-2-butenoate (**7b**)[17] were prepared by literature methods. All reactions were run under dry N_2 in oven-dried glassware. The HCl (0.2, 1, and 6 M), NaOH (0.2 and 1 M), $NaHCO_3$ (saturated), and NaCl (saturated) used

(13) See ref 8, p 986.

(14) Fletcher, R. J.; Lampard, C.; Murphy, J. A.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **1995**, 623−633.

(15) Sunitha, K.; Balasubramanian, K. K. *Tetrahedron* **1987**, *43*, 3269−3278.

(16) Attempts to perform the alkylation with ethyl (*E*)-4-bromo-2-butenoate in refluxing acetone resulted in alkylation and double-bond migration to give ethyl (*Z*)-4-(2-nitrophenyl)-3-butenoate. See: (a) Reference 15. (b) Balakumar, A.; Janardhanam, S.; Rajagopalan, K. *Indian J. Chem.* **1993**, *32B*, 313−317.

(17) Safaryn, J. E.; Chiarello, J.; Chen, K.-M.; Joullie, M. M. *Tetrahedron* **1986**, *42*, 2635−2642.

(18) Wittig reactions of α-alkoxyaldehydes with stabilized ylides in polar solvents (CH_3OH) have been found to give predominantly the *Z* olefin; see: Valverde, S.; Martin-Lomas, M.; Herradon, B.; Garcia-Ochoa, S. *Tetrahedron* **1987**, *43*, 1895−1901. In the current procedure, the crude aldehyde contained some residual methanol from the ozonolysis reaction and DMSO from the reductive workup procedure.

(19) Speziale, A. J.; Jaworski, E. G. *J. Org. Chem.* **1960**, *25*, 728−732.

(20) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.

(21) (a) Norman, R. O. C.; Coxon, J. M. *Principles of Organic Synthesis*, 3rd ed.; Chapman and Hall: New York, 1993; pp 666−668. (b) Use of 3−5 equiv of iron gave less consistent yields.

(22) See, for example: (a) Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *57*, 1727−1733. (b) Bunce, R. A.; Bennett, M. J. *Synth. Commun.* **1993**, *23*, 1009−1020.

(23) For reductions using activated iron, see: (a) Hazlet, S. E.; Dornfeld, C. A. *J. Am. Chem. Soc.* **1944**, *66*, 1781−1782. (b) Eisch, J. J.; Kovacs, C. A.; Rhee, S.-G. *J. Organomet. Chem.* **1974**, *65*, 289−301.

(24) For reductions using iron in the presence of acids, see: (a) Reference 7. (b) West, R. W. *J. Chem. Soc.* **1925**, *127*, 494−495. (c) Wertheim, E. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, pp 471−473. (d) Mosby, W. L. *J. Org. Chem.* **1959**, *24*, 421−423. (e) Wulfman, D. S.; Cooper, C. F. *Synthesis* **1978**, 924−925.

(25) Other mild conditions for nitroarene reductions have also been reported, but were not investigated for the current reaction; see: (a) Alper, H.; Gopal, M. *J. Chem. Soc., Chem. Commun.* **1980**, 821. (b) Sarmah, P.; Barua, N. C. *Tetrahedron Lett.* **1990**, *31*, 4065−4066. (c) Baruah, R. N. *Indian J. Chem.* **1994**, *33B*, 758. (d) Desai, D. G.; Swami, S. S.; Hapase, S. B. *Synth. Commun.* **1999**, *29*, 1033−1036. (e) Hari, A.; Miller, B. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2777−2779.

(26) For reductions using iron in the presence of added salts, see: (a) Lyons, R. E.; Smith, L. T. *Chem. Ber.* **1927**, *60*, 173−182. (b) Hodgson, H. H.; Whitehurst, J. S. *J. Chem. Soc.* **1945**, 202−204. (c) Senkus, M. *Ind. Eng. Chem.* **1948**, *40*, 506−508.

(27) Water containing $FeSO_4 \cdot 7H_2O$ (0.25 mmol/4.00 mL) was found to have a pH of 4. This appears to be sufficiently acidic to slowly cleave the allylic ethers.

(28) (a) Grandmougin, E. *Chem Ber.* **1906**, *39*, 3561−3564. (b) Fieser, L. F.; Fieser, M. *J. Am. Chem. Soc.* **1934**, *56*, 1565−1578.

in various procedures refer to aqueous solutions. Reactions were monitored by TLC on silica gel GF plates (Analtech no. 21521) or capillary GC (SE−30 column, 6 m × 0.25 mm i.d., 0.25 μm film thickness) with FI detection programmed between 50 and 300 °C. Preparative separations were performed using flash column chromatography on silica gel (grade 62, 60−200 mesh) mixed with Sylvania no. 2282 UV-active phosphor or PTLC on 20-cm × 20-cm silica gel GF plates (Analtech no. 02015); band elution was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

Representative Procedure for Alkylation of Methyl (2-Nitrophenyl)acetate: Methyl (±)-2-(2-Nitrophenyl)-4-pentenoate (2a). The general procedure of Makosza and Tyrala was used.[9] To a stirred solution of 1.95 g (10.0 mmol) of **1** in 50 mL of dry CH_3CN was added 11.6 g (84.1 mmol) of anhydrous K_2CO_3 and 15 mg of 18-crown-6. To the resulting blue mixture was added a solution of 2.02 g (1.10 mL, 12.0 mmol) of allyl iodide in 5 mL of CH_3CN and the reaction was stirred at reflux for 8 h. The solids were removed by filtration and the filtrate was concentrated under vacuum. The remaining oil was purified by flash chromatography on a 30 cm × 2.5 cm silica gel column eluted with increasing concentrations of ether in hexanes to give 2.16 g (9.19 mmol, 92%) of **2a** as a light yellow oil: IR 1736, 1641, 1532, 1350 cm^{-1}; ^{1}H NMR δ 7.90 (dd, J = 8.2, 1.4 Hz, 1 H), 7.62−7.51 (complex, 2 H), 7.43 (m, 1 H), 5.73 (ddt, J = 17.1, 10.1, 6.9 Hz, 1 H), 5.05 (dm, J = 17.1 Hz, 1 H), 5.01 (dm, J = 10.1 Hz, 1 H), 4.31 (t, J = 7.5 Hz, 1 H), 3.68 (s, 3 H), 2.91 (m, 1 H), 2.63 (m, 1 H); ^{13}C NMR δ 172.7, 149.5, 134.5, 133.1, 133.0, 130.2, 128.2, 124.8, 117.9, 52.2, 46.0, 36.8; HRMS m/z calcd for $C_{12}H_{13}NO_4$ 235.0844, found 235.0847.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.28; H, 5.53. Found: C, 61.54; H, 5.58.

Methyl (±)-4-methyl-2-(2-nitrophenyl)-4-pentenoate (2b): 2.30 g (9.24 mmol, 92%); IR 1744, 1650, 1530, 1353 cm^{-1}; ^{1}H NMR δ 7.88 (d, J = 8.2 Hz, 1 H), 7.58 (m, 2 H), 7.42 (m, 1 H), 4.75 (s, 1 H), 4.65 (s, 1 H), 4.48 (t, J = 7.5 Hz, 1 H), 3.67 (s, 3 H), 2.87 (dd, J = 14.4, 7.5 Hz, 1 H), 2.55 (dd, J = 14.4, 7.5 Hz, 1 H), 1.73 (s, 3 H); ^{13}C NMR δ 172.9, 149.5, 141.8, 133.1, 133.0, 130.0, 128.2, 124.7, 113.2, 52.0, 44.4, 40.7, 22.1; HRMS m/z calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.0998.

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02. Found: C, 62.78; H, 6.05.

Representative Procedure for Hydrolysis−Decarboxylation: 2-(3-Butenyl)-1-nitrobenzene (3a). The procedure of Bull and co-workers was used.[10] To a stirred solution of 8.50 g (36.1 mmol) of **2a** in 130 mL of dioxane was added 43.4 mL of 1 M NaOH, and the solution was stirred at room temperature for 3 h. The reaction was concentrated under vacuum, the solid was dissolved in 500 mL of water, and the solution was acidified to pH 2 with 6 M HCl. The milky suspension was extracted with ether (3×), and the combined ether layers were washed with NaCl (1×), dried ($MgSO_4$), and concentrated under vacuum to give 7.57 g (34.2 mmol) of the acid as a yellow solid. The crude acid was dissolved in 110 mL of dry DMF and treated with 4.72 g (34.2 mmol) of anhydrous K_2CO_3 at 50 °C for 45 min. The reaction mixture was cooled to room temperature, then poured into 300 mL of 0.2 M HCl and extracted with ether (2x). The combined ether layers were washed with NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum. The resulting brown oil was purified by flash chromatography on a 50 cm × 2.5 cm silica gel column eluted with 5% ether in hexane to give 5.86 g (33.1 mmol, 92%) of **3a** as a yellow oil: IR 1644, 1608, 1530, 1353 cm^{-1}; ^{1}H NMR δ 7.90 (dd, J = 8.2, 1.4 Hz, 1 H), 7.52 (m, 1 H), 7.36 (m, 2 H), 5.85 (ddt, J = 17.2, 10.2, 6.8 Hz, 1 H), 5.04 (dm, J = 17.2 Hz, 1 H), 5.01 (dm, J = 10.2 Hz, 1 H), 2.99 (t, J = 8.0 Hz, 2 H), 2.42 (m, 2 H); ^{13}C NMR δ 149.5, 137.2, 136.7, 132.9, 132.1, 127.1, 124.7, 115.8, 34.5, 32.4; HRMS m/z calcd for $C_{10}H_{11}NO_2$ 177.0790, found 177.0789.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.21. Found: C, 67.88; H, 6.22.

2-(3-Methyl-3-butenyl)-1-nitrobenzene (3b): 4.68 g (24.5 mmol, 92%); IR 1644, 1608, 1530, 1353 cm^{-1}; ^{1}H NMR δ 7.89 (dd, J = 8.4, 1.4 Hz, 1 H), 7.52 (td, J = 7.4, 1.4 Hz, 1 H), 7.34 (m, 2 H), 4.76 (s, 1 H), 4.71 (s, 1 H), 3.03 (t, J = 8.5 Hz, 2 H), 2.34 (t, J = 8.5 Hz, 2 H), 1.79 (s, 3 H); ^{13}C NMR δ 149.3, 144.5, 137.0, 132.8, 131.9, 127.0, 124.6, 110.9, 38.6, 31.5, 22.4; HRMS m/z calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0944.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81. Found: C, 69.05; H, 6.80.

Ozonolysis−Wittig Sequence: Ethyl (*E*)-5-(2-Nitrophenyl)-2-pentenoate (4a). A solution of 5.27 g (29.8 mmol) of **3a** in 200 mL of CH_3OH was treated with O_3 at −78 °C as described previously.[11] The crude aldehyde was diluted with benzene, 13.9 g (40.0 mmol) of (carbethoxymethylene)triphenylphosphorane was added, and the reaction was stirred at reflux for 8 h. The reaction was cooled and concentrated under vacuum to give a tan semisolid mass. The residue was layered on top of a 10 cm × 10 cm plug of silica gel in a sintered glass frit and 2 L of 15% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate gave the crude nitro acrylate as a viscous yellow oil. The oil was flash chromatographed on a 60 cm × 2.5 cm silica gel column eluted with increasing concentrations of ether in hexanes. The major band gave 4.15 g (16.7 mmol, 56%) of **4a** as a light yellow oil: IR 1723, 1659, 1530, 1353 cm^{-1}; ^{1}H NMR δ 7.94 (dd, J = 8.1, 1.4 Hz, 1 H), 7.55 (td, J = 7.5, 1.4 Hz, 1 H), 7.42−7.33 (complex, 2 H), 7.01 (dt, J = 15.7, 6.9 Hz, 1 H), 5.86 (dt, J = 15.7, 1.5 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 3.03 (t, J = 7.7 Hz, 2 H), 2.58 (m, 2 H), 1.29 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 166.5, 149.1, 147.0, 135.9, 133.2, 132.0, 127.6, 125.0, 122.5, 60.2, 32.8, 31.7, 14.1; HRMS m/z calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.1004.

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02. Found: C, 62.90; H, 6.07.

Ethyl (*Z*)-4-(2-nitrophenoxy)-2-butenoate (8a*Z*): 5.27 g (21.0 mmol, 52%); mp 32−34 °C; IR 1716, 1659, 1530, 1352 cm^{-1}; ^{1}H NMR δ 7.85 (dd, J = 8.1, 1.6 Hz, 1 H), 7.53 (m, 1 H), 7.11 (d, J = 8.5 Hz, 1 H), 7.05 (m, 1 H), 6.54 (dt, J = 11.6, 4.7 Hz, 1 H), 5.97 (dt, J = 11.6, 2.5 Hz, 1 H), 5.31 (dd, J = 4.7, 2.5 Hz, 2 H), 4.22 (q, J = 7.1 Hz, 2 H), 1.33 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 166.1, 151.7, 145.1, 140.1, 134.2, 125.8, 120.8, 120.7, 114.7, 67.7, 60.6, 14.1; HRMS m/z calcd for $C_{12}H_{13}NO_5$ 251.0793, found 251.0795.

Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.18. Found: C, 57.59; H, 5.24.

Ozonolysis−Wadsworth−Emmons Sequence: Ethyl (*E*)-3-Methyl-5-(2-nitrophenyl)-2-pentenoate (4b). Following ozonolysis of 3.03 g (15.9 mmol) of **3b** in 150 mL of CH_3OH as above, 5.08 g (6.00 mL, 84.9 mmol) of dimethyl sulfide and 200 mg of *p*-TsOH were added. The reaction was warmed to room temperature and stirred for 8 h. After concentration, the residue was dissolved in ether, washed with $NaHCO_3$ (2×) and NaCl (1×), dried ($MgSO_4$), and concentrated under vacuum. Flash chromatography on a 30 cm × 2 cm silica gel column eluted with increasing concentrations of ether in hexanes gave 2.80 g (14.5 mmol, 91%) of 4-(2-nitrophenyl)-2-butanone as a light yellow oil: IR 1715, 1530, 1352 cm^{-1}; ^{1}H NMR δ 7.93 (dd, J = 8.1, 1.3 Hz, 1 H), 7.53 (td, J = 7.5, 1.3 Hz, 1 H), 7.42−7.28 (complex, 2 H), 3.15 (ABt, J = 7.4 Hz, 2 H), 2.86 (ABt, J = 7.4 Hz, 2 H), 2.17 (s, 3 H); ^{13}C NMR δ 207.0, 149.4, 136.2, 133.2, 132.4, 127.4, 124.8, 44.1, 29.8, 27.2.

Using the procedure of Balsevich,[12] 2.00 g (10.3 mmol) of the ketone was reacted with 2.29 g (11.7 mmol) of ethyl dimethylphosphonoacetate in THF−DMSO to give the crude nitro acrylate. Flash chromatography on a 40 cm × 2 cm silica gel column eluted with increasing concentrations of ether in hexanes gave 1.81 g (6.89 mmol, 67%) of **4b** as a light yellow oil: IR 1716, 1651, 1530, 1353 cm^{-1}; ^{1}H NMR δ 7.94 (dd, J = 8.2, 1.4 Hz, 1 H), 7.54 (td, J = 7.5, 1.4 Hz, 1 H), 7.40−7.31 (complex, 2 H), 5.70 (q, J = 1.3 Hz, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.06 (m, 2 H), 2.47 (m, 2 H), 2.24 (d, J = 1.3 Hz, 3 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 166.6, 157.9, 149.2, 136.1, 133.1, 132.0, 127.4, 124.9, 116.6, 59.6, 41.7, 31.6, 18.8, 14.3; HRMS m/z calcd for $C_{14}H_{17}NO_4$ 263.1157, found 263.1156.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.88; H, 6.46. Found: C, 63.96; H, 6.43.

Representative Procedure for Alkylation of 2-Nitrophenol: Ethyl (*E*)-4-(2-Nitrophenoxy)-2-butenoate (8a*E*). A mixture of 2.76 g (20.0 mmol) of **5** and 2.76 g (20.0 mmol) of anhydrous K_2CO_3 was treated with 3.86 g (20.0 mmol) of **7a** in 75 mL of dry acetone at 0−20 °C according to the procedure of

Sunitha and Balasubramanian.[15] Following workup, the resulting solid was recrystallized from ether-pentane to give 2.91 g (11.6 mmol, 58%) of pure **8a***E*: mp 56−58 °C; IR 1717, 1662, 1530, 1353 cm^{-1}; ^1H NMR δ 7.89 (dd, J = 8.1, 1.6 Hz, 1 H), 7.54 (m, 1 H), 7.11−7.02 (complex, 3 H), 6.30 (dt, J = 15.7, 2.1 Hz, 1 H), 4.85 (dd, J = 3.8, 2.1 Hz, 2 H), 4.22 (q, J = 7.1 Hz, 2 H), 1.31 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 165.9, 151.3, 140.3, 140.1, 134.2, 125.9, 122.8, 121.1, 114.5, 67.7, 60.7, 14.2; HRMS *m/z* calcd for $C_{12}H_{13}NO_5$ 251.1079, found 251.1075.

Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.18. Found: C, 57.53; H, 5.21.

Ethyl (*E*)-3-methyl-4-(2-nitrophenoxy)-2-butenoate (8b*E*): 1.48 g (5.60 mmol, 40%; 55% based on recovered **7b**); mp 71−72 °C; IR 1716, 1666, 1530, 1353 cm^{-1}; ^1H NMR δ 7.88 (dd, J = 8.1, 1.6 Hz, 1 H), 7.53 (m, 1 H), 7.08 (m, 1 H), 7.03 (dd, J = 8.4, 1.0 Hz, 1 H), 6.12 (sextet, J = 1.5 Hz, 1 H), 4.63 (d, J = 1.5 Hz, 2 H), 4.18 (q, J = 7.1 Hz, 2 H), 2.22 (d, J = 1.5 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 166.3, 151.4, 150.6, 148.5, 134.2, 125.9, 121.0, 116.6, 114.6, 72.6, 60.0, 15.5, 14.2; HRMS *m/z* calcd for $C_{13}H_{15}NO_5$ 265.0950, found 265.0948.

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66. Found: C, 59.05; H, 5.71.

Representative Procedure for Alkylation of 2-Nitroaniline: Ethyl (*E*)-4-((2-Nitrophenyl)amino)-2-butenoate (10a). A mixture of 6.90 g (50.0 mmol) of **9** and 4.82 g (25.0 mmol) of **7a** was heated with stirring at 100 °C for 12 h.[19] The reaction was cooled and the solid transferred to a separatory funnel with the aid of ether and CH_2Cl_2. The organic layer was washed with $NaHCO_3$ (6×) and NaCl (1×), dried ($MgSO_4$), and concentrated under vacuum. The solid was purified on a 100 cm × 2.5 cm silica gel column eluted with 5−10% ether in hexanes to give 4.69 g (18.8 mmol, 75%) of pure **10a**: mp 50−51 °C; IR 3388, 1716, 1662, 1528, 1351 cm^{-1}; ^1H NMR δ 8.26 (br s, 1 H), 8.20 (dd, J = 8.5, 1.6 Hz, 1 H), 7.44 (m, 1 H), 7.03 (dt, J = 15.7, 4.4 Hz, 1 H), 6.74 (d, J = 8.8 Hz, 1 H), 6.72 (m, 1 H), 6.02 (dt, J = 15.7, 2.1 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.18 (m, 2 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 165.8, 144.7, 143.0, 136.3, 132.9, 126.9, 122.5, 116.2, 113.8, 60.6, 43.6, 14.2; HRMS *m/z* calcd for $C_{12}H_{14}N_2O_4$ 250.0954, found 250.0950.

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.60; H, 5.60. Found: C, 57.69; H, 5.66.

Ethyl (*E*)-3-methyl-4-((2-nitrophenyl)amino)-2-butenoate (10b): 1.60 g (6.06 mmol, 70%); mp 69−70 °C; IR 3389, 1715, 1666, 1516, 1353 cm^{-1}; ^1H NMR δ 8.31 (br t, J = 5.5 Hz, 1 H), 8.20 (dd, J = 8.5, 1.4 Hz, 1 H), 7.43 (m, 1 H), 6.71 (m, 1 H), 6.68 (d, J = 8.6 Hz, 1 H), 5.84 (q, J = 1.4 Hz, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.00 (d, J = 5.5 Hz, 2 H), 2.22 (d, J = 1.4 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 166.3, 153.3, 148.5, 144.9, 136.3, 126.9, 116.2, 115.6, 113.9, 59.9, 50.1, 16.7, 14.2; HRMS *m/z* calcd for $C_{13}H_{16}N_2O_4$ 264.1110, found 264.1112.

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.09; H, 6.06. Found: C, 59.14; H, 6.09.

Representative Procedure for Tandem Reduction−Michael Addition: Ethyl (±)-1,2,3,4-Tetrahydroquinoline-2-acetate (11a). A 100-mL three-necked round-bottomed flask, equipped with a reflux condenser (N_2 inlet) and a magnetic stirrer was charged with 4.0 mL of acetic acid, 249 mg (1.00 mmol) of **4a**, and 335 mg (6.00 mmol) of iron powder (>100 mesh). The reaction was heated with stirring at 115 °C (oil bath temperature 120 °C) for 30 min and then cooled. The crude reaction mixture was diluted with 50 mL of ether, transferred to a separatory funnel, and cautiously washed with $NaHCO_3$ (5×). The aqueous washes were back-extracted with ether (1×), and the combined ether layers were washed with NaCl (1×), dried ($MgSO_4$), and concentrated under vacuum. The resulting yellow oil was purified by PTLC eluted with 15% ether in hexanes to give 215 mg (0.98 mmol, 98%) of **11a** as a light yellow oil: IR 3395, 1729 cm^{-1}; ^1H NMR δ 6.97 (m, 2 H), 6.60 (td, J = 7.3, 1.1 Hz, 1 H), 6.50 (dd, J = 8.2, 1.3 Hz, 1 H), 4.48 (br s, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 3.72 (m, 1 H), 2.89−2.68 (complex, 2 H), 2.50 (m, 2 H), 1.96 (dm, J = 9.6 Hz, 1 H), 1.71 (m, 1 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 172.3, 144.0, 129.2, 126.8, 120.8, 117.3, 114.5, 60.6, 47.8, 40.9, 28.0, 25.6, 14.2; HRMS *m/z* calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1259.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.29; H, 7.77; N, 6.42.

Ethyl (±)-2-methyl-1,2,3,4-tetrahydroquinoline-2-acetate (11b): 207 mg (0.89 mmol, 89%); IR 3395, 1730 cm^{-1}; ^1H NMR δ 6.98 (m, 2 H), 6.63 (td, J = 7.4, 1.2 Hz, 1 H), 6.51 (dd, J = 8.2, 1.2 Hz, 1 H), 4.63 (br s, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 2.78 (t, J = 6.8 Hz, 2 H), 2.55 (ABd, J = 14.8 Hz, 1 H), 2.43 (ABd, J = 14.8 Hz, 1 H), 1.78 (m, 2 H), 1.29 (d, J = 0.5 Hz, 3 H), 1.27 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 171.9, 143.3, 129.3, 126.9, 119.8, 117.1, 114.9, 60.3, 50.0, 44.5, 34.0, 26.0, 23.5, 14.2; HRMS *m/z* calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1417.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found: C, 72.37; H, 8.19; N, 5.98.

Ethyl (±)-3,4-dihydro-2*H*-1,4-benzoxazine-3-acetate (11c): 208 mg (0.94 mmol, 94%) from **8a***E*; 216 mg (0.98 mmol, 98%) from **8a***Z*; mp 24−25 °C; IR 3360, 1730 cm^{-1}; ^1H NMR δ 6.77 (m, 2 H), 6.68−6.58 (complex, 2 H), 4.20 (dd, J = 10.6, 2.6 Hz, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 3.96 (dd, J = 10.6, 6.0 Hz, 1 H), 3.84 (m, 1 H), 3.66 (br s, 1 H), 2.53 (m, 2 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 171.6, 143.5, 132.5, 121.7, 118.9, 116.5, 115.7, 68.4, 60.7, 46.2, 36.7, 14.2; HRMS *m/z* calcd for $C_{12}H_{15}NO_3$ 221.1052, found 221.1049.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.16; H, 6.79; N, 6.33. Found: C, 65.29; H, 6.83; N, 6.28.

Ethyl (±)-3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-3-acetate (11d): 207 mg (0.88 mmol, 88%); IR 3381, 1730 cm^{-1}; ^1H NMR δ 6.79 (m, 2 H), 6.66−6.58 (complex, 2 H), 4.55 (br s, 1 H), 4.18 (qd, J = 7.1, 1.0 Hz, 2 H), 3.96 (ABd, J = 10.6 Hz, 1 H), 3.86 (ABd, J = 10.6 Hz, 1 H), 2.69 (ABd, J = 15.7 Hz, 1 H), 2.43 (ABd, J = 15.7 Hz, 1 H), 1.30 (d, J = 0.5 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 171.6, 142.7, 132.3, 121.8, 118.6, 116.4, 115.8, 73.1, 60.5, 48.9, 40.5, 22.4, 14.2; HRMS *m/z* calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1208.

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.96. Found: C, 66.54; H, 7.25; N, 6.01.

Ethyl (±)-1,2,3,4-tetrahydroquinoxaline-2-acetate (11e): 196 mg (0.89 mmol, 89%); IR 3385, 1728 cm^{-1}; ^1H NMR δ 6.60 (m, 2 H), 6.52 (m, 2 H), 4.21 (br s, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 3.84 (m, 1 H), 3.67 (br s, 1 H), 3.40 (dd, J = 10.9, 3.0 Hz, 1 H), 3.13 (dd, J = 10.9, 6.3 Hz, 1 H), 2.55 (m, 2 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 172.1, 132.9, 132.7, 119.0, 118.7, 114.8, 114.5, 60.7, 46.7, 45.7, 38.7, 14.2; HRMS *m/z* calcd for $C_{12}H_{16}N_2O_2$ 220.1212, found 220.1208.

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.45; H, 7.27; N, 12.73. Found: C, 65.62; H, 7.31; N, 12.78.

Ethyl (±)-2-methyl-1,2,3,4-tetrahydroquinoxaline-2-acetate (11f): 202 mg (0.86 mmol, 86%); mp 45−46 °C; IR 3388, 1730 cm^{-1}; ^1H NMR δ 6.60 (m, 2 H), 6.51 (m, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.03 (br s, 2 H), 3.13 (br s, 2 H), 2.68 (ABd, J = 15.4 Hz, 1 H), 2.43 (ABd, J = 15.4 Hz, 1 H), 1.29 (d, J = 0.5 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 172.0, 132.2, 132.1, 119.0, 118.6, 115.0, 114.3, 60.3, 51.3, 49.0, 42.4, 24.4, 14.2; HRMS *m/z* calcd for $C_{13}H_{18}N_2O_2$ 234.1369, found 234.1367.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.67; H, 7.69; N, 11.97. Found: C, 66.79; H, 7.71; N, 12.05.

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