1-Alkyl-2,3-dihydro-4(1*H*)-quinolinones by a Tandem Michael-S_NAr Annulation Reaction

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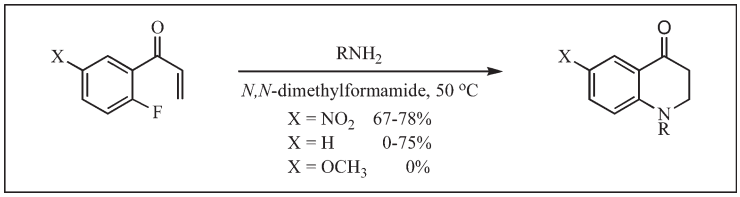

A tandem Michael-S_NAr annulation reaction has been developed for the synthesis of 1-alkyl-2,3-dihydro-4(1*H*)-quinolinones. Success in the reaction followed expected electronic effects for the final S_NAr ring closure. Treatment of doubly activated 1-(2-fluoro-5-nitrophenyl)-2-propen-1-one with primary amines in *N,N*-dimethylformamide at 50°C for 24 h provided 2,3-dihydro-4(1*H*)-quinolinones in 67–78% yields. Singly activated 1-(2-fluorophenyl)-2-propen-1-one reacted similarly, but failed to undergo the final ring closure with hindered or aromatic amines. Finally, 1-(2-fluoro-5-methoxyphenyl)-2-propen-1-one, with one activating and one deactivating group on the ring, gave only simple 1,4-addition products.

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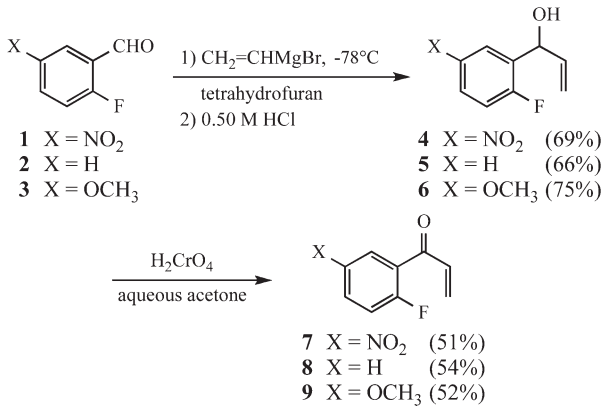
INTRODUCTION

Over the past several years, our work has led to a number of tandem cyclizations terminated by nucleophilic aromatic substitution reactions [2]. The current work extends these previous results to the preparation of 1-alkyl-2,3-dihydro-4(1*H*)-quinolinones by a sequential Michael-S_NAr process. Earlier approaches to these ring systems have involved Friedel-Crafts cyclizations of *N*-phenyl-β-alanine derivatives [3]; acid mediated ring opening-Friedel-Crafts reactions of 1-aryl-2-azetidinones [4]; acid or base promoted cyclizations of 2-aminochalcone derivatives [5]; or reaction of aromatic amines with iminium salts derived from reaction of *N,N*-dimethylacrylamide with trifluoromethanesulfonic anhydride [6]. These protocols gave modest to good yields, but generally subjected substrates to strongly acidic reagents. The current reaction provides a straightforward route to the title compounds in good yields under very mild reaction conditions. The target dihydroquinolinones are valuable building blocks for the synthesis of drugs used to treat pain [7], psychosis [8], and Alzheimer's disease [9] as well as several other medical afflictions [10].

RESULTS AND DISCUSSION

The synthesis of our cyclization substrates is shown in Scheme 1. The requisite aryl vinyl ketones were easily prepared in two steps from 2-fluoro-5-nitrobenzaldehyde (**1**) [11], 2-fluorobenzaldehyde (**2**), and 2-fluoro-5-methoxybenzaldehyde (**3**). Treatment of these aldehydes with vinylmagnesium bromide in tetrahydrofuran at −78°C gave alcohols **4**, **5**, and **6**, respectively. These alcohols were carried on directly to dihydroquinolinone precursors **7**, **8**, and **9** by Jones oxidation in 34–39% overall yields after chromatography [12].

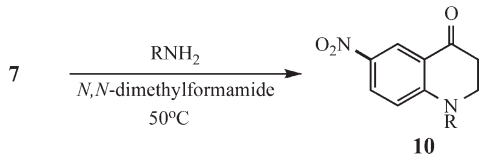
Scheme 1



In the planning stages, we anticipated that 1,4-addition to the unhindered side chain enone would precede nucleophilic attack on the aromatic ring. Because of this, however, bulky amines could pose a problem in the final S_NAr ring closure. Thus, precursor **7** was selected as our initial test case because this compound possessed two electron-withdrawing substituents positioned to facilitate the final ring-closing step. If the annulation proceeded

Table 1

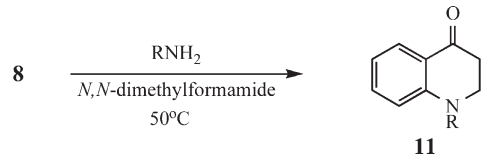
Michael-S_NAr reaction of a doubly activated substrate.



	R	Yield (%)
a	$C_6H_5CH_2$	69
b	$C_6H_5CH_2CH_2$	78
c	*n*-C_6H_{13}	67
d	*i*-$C_3H_7OCH_2CH_2CH_2$	75
e	*i*-C_4H_9	72
f	*c*-C_6H_{11}	77
g	*t*-C_4H_9	71
h	C_6H_5	72

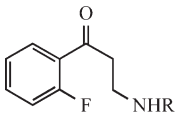
Table 2

Michael-S_NAr reaction of a singly activated substrate.



	R	Yield (%)
a	$C_6H_5CH_2$	61
b	$C_6H_5CH_2CH_2$	58
c	*n*-C_6H_{13}	74
d	*i*-$C_3H_7OCH_2CH_2CH_2$	70
e	*i*-C_4H_9	75
f	*c*-C_6H_{11}	54
g	*t*-C_4H_9	0[a]
h	C_6H_5	0[b]

[a] This reaction gave 3-(*tert*-butylamino)-1-(2-fluorophenyl)-1-propanone (**12a**) as the only product in 52% yield.
[b] This reaction gave 1-(2-fluorophenyl)-3-(phenylamino)-1-propanone (**12b**) as the only product in 65% yield.



12a R = *t*-C_4H_9
12b R = C_6H_5

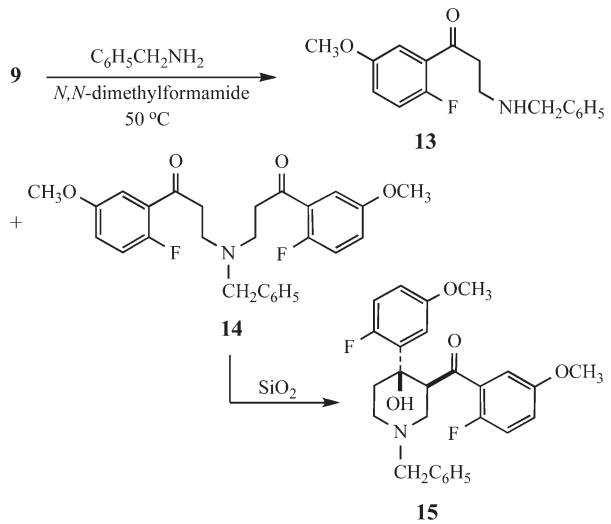
smoothly for **7**, we planned to further explore the scope of the reaction by studying compounds **8** and **9**, which vary the electronic nature of the aromatic moiety. Substrate **8** has a single activating group for the final S_NAr reaction; **9** has one activating and one deactivating group.

Experimentally, the Michael-S_NAr reaction was carried out by dissolving 1.00 equivalent of the aryl vinyl ketone in dry *N*,*N*-dimethylformamide, adding 1.25 equivalents of the amine and heating for 24 h at 50°C. Following workup, the products were easily isolated and purified by chromatography to give the target heterocycles in good yields. The use of *N*,*N*-dimethylformamide as the solvent was critical to the success of the reaction; methanol gave complex product mixtures and was not useful.

The results of our cyclization studies are summarized in Tables 1 and 2. Doubly activated substrate **7** reacted with α-branched as well as unbranched and aryl primary amines to give dihydroquinolinones in 67–78% yields. Singly activated precursor **8** was successful in most cases, but failed to cyclize with sterically hindered amines such as *tert*-butylamine and deactivated amines such as aniline. The methoxy-bearing substrate **9** afforded products derived only from 1,4-addition without the subsequent ring closure. Thus, under our standard conditions with benzylamine, **9** gave the expected 1:1 Michael adduct **13** in 12% yield (Scheme 2). More surprisingly, however, the reaction also produced piperidinol **15** in 42% yield. This product presumably arose from silica gel-promoted aldol ring closure of the 2:1 Michael adduct **14** during chromatography. Indeed, ^1H NMR analysis of the crude reaction mixture revealed that **14** was present before purification. The structure of **15** was deduced from spectral analysis and by comparison to calculated ^1H and ^{13}C NMR spectra [13], but the stereochemical assignment is tentative. The indicated relative stereochemistry places both aryl moieties in equatorial positions and allows hydrogen bonding between the C1 alcohol and the side chain carbonyl.

Thus, for success in the two-reaction sequence, the substrate must possess at least one electron-withdrawing group ortho or para to fluorine on the aromatic ring. Substrates incorporating an electron-donating group on the ring (even in the presence of a second withdrawing

Scheme 2



substituent) fail to undergo the final ring closure. Additionally, the reacting partner must be an alkyl or aryl primary amine. Secondary amines give only complex product mixtures containing low yields of the 1,4-adduct.

The mechanism of dihydroquinolinone formation involves sequential Michael addition to the side chain enone followed by S_NAr ring closure. The fact that hindered and deactivated amines react with **8** to afford only the simple 1,4-addition product confirms this reaction sequence. Uncyclized structures resulting from an initial S_NAr reaction with the aromatic ring are not observed, nor are products resulting from attack at the carbonyl.

CONCLUSION

We have developed a new approach to the synthesis of 1-alkyl-2,3-dihydro-4(1*H*)-quinolinones based on a novel tandem Michael addition-S_NAr reaction. The required substrates are easily prepared in two steps from readily available precursors. The sequence gives good yields of the target ring system from substrates having either one or two electron withdrawing groups ortho or para to fluorine on the aromatic ring. Systems having one activating group are slightly less reactive while those incorporating an electron donating group give only Michael adducts and fail to close the final ring. We are pursuing further studies of this annulation procedure in systems bearing alkyl groups at the β-carbon of the Michael acceptor.

EXPERIMENTAL

All reactions were run under dry nitrogen. Vinylmagnesium bromide (1*M* in tetrahydrofuran) was purchased from Aldrich Chemical Company. *N*,*N*-Dimethylformamide from a freshly opened bottle was stored over 4 Å molecular sieves and syringed into reactions where it was used. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521) with ultraviolet detection. The 0.5*M* hydrochloric acid, saturated sodium bisulfite, saturated sodium chloride, and 0.1*M* sodium hydroxide used in workup procedures were aqueous solutions. Preparative separations were performed by one of the following methods: (1) flash column chromatography [14] on silica gel (grade 62, 60–200 mesh) containing ultraviolet-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 both methods was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65–70°C. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (*J*) are given in Hertz. Unless otherwise indicated, mass spectra (electron impact/direct probe) were obtained at 70 eV.

Representative procedure for the addition of vinylmagnesium bromide: (±)-1-(2-Fluoro-5-nitrophenyl)-2-propen-1-ol (4). The general procedure of Danishefsky and coworkers was used [11]. To a −78°C solution of 4.00 g (23.7 mmoles) of **1** [11] in 75 mL of anhydrous tetrahydrofuran was added 35.6 mL of 1*M* vinylmagnesium bromide in tetrahydrofuran (35.6 mmoles). The reaction mixture was stirred for 3.5 h at −78°C, then quenched by addition of 50 mL of 0.5*M* hydrochloric acid and ether extracted (three times). The combined ether extracts were washed with water (three times), saturated sodium chloride (one time), dried (magnesium sulfate), and concentrated under vacuum to give 3.09 g (66%) of **4** as a brown oil. This product was spectroscopically pure and was used without further purification. IR: 3382, 1530, 1353, 1254 cm^{-1}; ^{1}H NMR: δ 8.44 (dd, 1H, J = 6.1, 2.9), 8.18 (ddd, 1H, J = 9.0, 4.4, 2.9), 7.18 (t, 1H, J = 9.0), 6.02 (ddd, 1H, J = 17.2, 10.3, 6.0), 5.55 (d, 1H, J = 6.0), 5.43 (d, 1H, J = 17.2), 5.28 (d, 1H, J = 10.3), 2.53 (br s, 1H); ^{13}C NMR: δ 163.1 (d, J = 257.9), 144.7, 137.7, 131.8 (d, J = 16.0), 125.0 (d, J = 10.3), 123.8 (d, J = 6.6), 116.7, 116.4 (d, J = 24.6), 68.5 (d, J = 2.3); ms (30 eV): *m*/*z* 197 (M^+). Anal. Calcd. for $C_9H_8FNO_3$: C, 54.82; H, 4.06; N, 7.11. Found: C, 54.89; H, 4.10; N, 7.02.

(±)-1-Phenyl-2-propen-1-ol (5). This compound (3.10 g, 69%) was prepared as above from 3.66 g (29.6 mmoles) of **2** and 30 mL of 1*M* vinylmagnesium bromide (30.0 mmoles). It was used without further purification. IR: 3363, 1228 cm^{-1}; ^{1}H NMR: δ 7.43 (td, 1H, J = 7.4, 1.6), 7.25 (m, 1H), 7.14 (td, 1H, J = 7.6, 1.0), 7.02 (ddd, 1H, J = 10.3, 8.2, 1.0), 6.06 (ddd, 1H, J = 17.2, 10.3, 5.5), 5.50 (d, 1H, J = 5.5), 5.34 (d, 1H, J = 17.2), 5.19 (dd, 1H, J = 10.3, 1.2), 2.47 (br s, 1H); ^{13}C NMR: δ 159.9 (d, J = 246.6), 138.8, 129.6, (d, J = 13.3), 129.2, (d, J = 8.1), 127.6 (d, J = 3.7), 124.3 (d, J = 3.7), 115.3 (d, J = 22.1), 115.3, 69.1 (d, J = 2.9); ms (30 eV): *m*/*z* 152 (M^+). Anal. Calcd. for C_9H_9FO: C, 71.05; H, 5.92. Found: C, 71.08; H, 5.93.

(±)-1-(2-Fluoro-5-methoxyphenyl)-2-propen-1-ol (6). This compound (2.21 g, 75%) was prepared as above from 2.50 g (16.2 mmoles) of **3** and 24.5 mL of 1*M* vinylmagnesium bromide (24.5 mmoles). It was used without further purification. IR: 3402, 2839, 1272 cm^{-1}; ^{1}H NMR: δ 6.97 (m, 1H), 6.95 (t, 1H, J = 9.0), 6.76 (ddd, 1H, J = 9.0, 3.8, 3.3), 6.05 (ddd, 1H, J = 16.4, 10.0, 5.5), 5.48 (d, 1H, J = 5.5), 5.35 (dd, 1H, J = 17.3, 0.8), 5.20 (dt, 1H, J = 1.0, 1.1), 3.78 (s, 3H), 2.27 (br s, 1H); ^{13}C NMR: δ 155.8, 154.3 (d, J = 238.8), 138.7, 130.3 (d, J = 14.9), 115.9 (d, J = 23.5), 115.4, 114.2 (d, J = 8.3), 112.2 (d, J = 4.0), 69.2, 55.7; ms (30 eV): *m*/*z* 182 (M^+). Anal. Calcd. for $C_{10}H_{11}FO_2$: C, 65.93; H, 6.04. Found: C, 66.01; H, 6.10.

Representative procedure for oxidation to the enone: 1-(2-Fluoro-5-nitrophenyl)-2-propen-1-one (7). The general procedure of Danishefsky and coworkers was used [12]. To a solution of 3.09 g (15.7 mmoles) of **4** in 30 mL of acetone was added 8.10 mL of freshly prepared Jones reagent (*ca*., 2.9*M*, 23.5 mmoles) [15]. After 15 min, 37.5 mL of ice water was added followed by 7.5 mL of saturated sodium bisulfite and the resulting mixture was extracted with ether (four times). The combined ether extracts were washed with water (three times), saturated sodium chloride (one time), dried (magnesium sulfate), and concentrated under vacuum. The resulting yellow oil was flash chromatographed on a 40 cm × 2.5 cm silica gel column eluted with 5–15% ether in hexanes to give 1.57 g (51%) of **7** as a light yellow oil that crystallized on standing, mp 50–52°C. IR: 1673, 1530, 1349, 1251 cm^{-1}; ^{1}H NMR: δ 8.65 (dd, 1H, J = 6.1, 2.9), 8.42 (ddd, 1H, J = 9.0, 4.1, 2.9), 7.35 (t, 1H, J = 9.0), 7.01 (ddd, 1H, J = 17.2, 10.3,

3.0), 6.45 (dt, 1H, J = 17.2, 1.2), 6.06 (dd, 1H, J = 10.3, 1.2); ^{13}C NMR: δ 187.1 (d, J = 2.9), 164.1 (d, J = 264.3), 144.4, 134.4 (d, J = 5.9), 132.2, 129.0 (d, J = 11.0), 127.0 (d, J = 16.2), 127.0 (d, J = 5.2), 118.0 (d, J = 25.8); ms (30 eV): m/z 195. Anal. Calcd. for $C_9H_6FNO_3$: C, 55.38; H, 3.08; N, 7.18. Found: C, 55.44; H, 3.11; N, 7.15.

1-Phenyl-2-propen-1-one (8). This compound was prepared as a colorless oil from 3.10 g (20.3 mmoles) of **5** and 10.5 mL of freshly prepared Jones reagent (*ca*., 2.9*M*, 30.4 mmoles) [15]. The crude product was flash chromatographed on a 40 cm × 2.5 cm silica gel column eluted with 5% ether in hexanes to give 1.64 g (54%) of **8** as a colorless oil. IR: 1673, 1276 cm^{-1}; ^{1}H NMR: 7.75 (td, 1H, J = 7.4, 1.8), 7.51 (m, 1H), 7.24 (td, 1H, J = 7.6, 1.0), 7.14 (ddd, 1H, J = 10.7, 8.4, 1.0), 7.02 (ddd, 1H, J = 17.2, 10.4, 3.1), 6.39 (dt, 1H, J = 17.2, 1.6), 5.92 (dd, 1H, J = 10.4, 1.6); ^{13}C NMR: δ 189.6, 161.2 (d, J = 254.0), 135.5 (d, J = 5.9), 134.1 (d, J = 8.8), 130.9 (d, J = 2.9), 130.2, 128.3, 124.4 (d, J = 2.9), 116.5 (d, J = 22.8); ms (30 eV): m/z 150 (M^+). Anal. Calcd. for C_9H_7FO: C, 72.00; H, 4.67. Found: C, 72.04; H, 4.69.

1-(2-Fluoro-5-methoxyphenyl)-2-propen-1-one (9). This compound was prepared from 2.21 g (12.1 mmoles) of **6** and 6.86 mL of freshly prepared Jones reagent (*ca*., 2.9*M*, 19.9 mmoles) [15]. The crude product was flash chromatographed on a 40 cm × 2.5 cm silica gel column eluted with 5% ether in hexanes to give 1.14 g (52%) of **9** as a colorless oil. IR: 2840, 1671, 1273 cm^{-1}; ^{1}H NMR: δ 7.24 (m, 1H), 7.10–6.99 (complex, 3H), 6.41 (dt, 1H, J = 17.0, 1.6), 5.91 (dd, 1H, J = 10.4, 1.6), 3.82 (s, 3H); ^{13}C NMR: δ 189.2, 155.9 (d, J = 246.8), 155.8, 135.4 (d, J = 7.2), 130.1, 126.3 (d, J = 15.9), 120.8 (d, J = 8.6), 117.4 (d, J = 25.4), 113.6 (d, J = 2.9), 55.9; ms (30 eV): m/z 180 (M^+). Anal. Calcd. for $C_{10}H_9FO_2$: C, 66.67; H, 5.00. Found: C, 66.71; H, 5.03.

Representative procedure for the tandem Michael-S_NAr reaction using 7: 1-Benzyl-6-nitro-4(1*H*)-quinolinone (10a). To a solution of 78 mg (0.4 mmoles) of **5** in 3 mL of anhydrous *N*,*N*-dimethylformamide was added 53.5 mg (0.055 mL, 0.5 mmoles) of benzylamine and the solution was heated at 50°C for 22 h. The reaction mixture was cooled and added to 25 mL of saturated sodium chloride and extracted with ether (three times). The combined ether extracts were washed with water (one time), saturated sodium chloride (one time), dried (magnesium sulfate), and concentrated under vacuum to afford a dark yellow oil. The product was purified on a 20-cm × 20-cm preparative thin layer chromatography plate using 50–70% ether in hexanes to afford 78 mg (69%) of **7a** as a yellow solid, mp 118–121°C. IR: 1686, 1513, 1314 cm^{-1}; ^{1}H NMR: δ 8.77 (d, 1H, J = 2.7), 8.11 (dd, 1H, J = 9.5, 2.7), 7.43–7.28 (complex, 3H), 7.25 (d, 2H, J = 7.0), 6.74 (d, 1H, J = 9.5), 4.72 (s, 2H), 3.77 (t, 2H, J = 7.1), 2.83 (t, 2H, J = 7.1); ^{13}C NMR: δ 191.2, 154.5, 138.3, 135.2, 130.0, 129.2, 128.0, 126.5, 125.1, 118.1, 113.3, 55.4, 49.0, 37.1; ms: m/z 191 (M^+-C_7H_7). Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.09; H, 4.96; N, 9.93. Found: C, 68.05; H, 4.95; N, 9.96.

6-Nitro-1-(2-phenylethyl)-4(1*H*)-quinolinone (10b). This compound (92 mg, 78%) was isolated as a yellow solid, mp 96–99°C. IR: 1687, 1517, 1317 cm^{-1}; ^{1}H NMR: δ 8.74 (s, 1H), 8.17 (d, 1H, J = 9.2), 7.38–7.18 (complex, 5H), 6.73 (d, 1H, J = 9.2), 3.76 (t, 2H, J = 6.8), 3.49 (t, 2H, J = 7.0), 2.98 (t, 2H, J = 7.0), 2.59 (t, 2H, J = 7.0); ^{13}C NMR: δ 191.3, 153.7, 137.9, 137.6, 129.9, 128.9, 128.7, 127.1, 125.4, 117.9, 112.5, 53.8, 49.2, 36.7, 33.2; ms: m/z 205 (M^+-C_7H_7). Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.41; N, 9.46. Found: C, 68.94; H, 5.40; N, 9.49.

1-Hexyl-6-nitro-4(1*H*)-quinolinone (10c). This compound (74 mg, 67%) was isolated as a yellow oil. IR: 1688, 1515, 1317 cm^{-1}; ^{1}H NMR: δ 8.73 (d, 1H, J = 2.7), 8.17 (dd, 1H, J = 9.4, 2.7), 6.71 (d, 1H, J = 9.4), 3.68 (t, 2H, J = 7.0), 3.48 (t, 2H, J = 7.4), 2.76 (t, 2H, J = 7.0), 1.68 (quintet, 2H, J = 7.4), 1.41–1.33 (complex, 6H), 0.91 (t, 3H, J = 6.8); ^{13}C NMR: δ 191.3, 154.1, 137.4, 129.9, 125.3, 117.8, 112.6, 52.1, 48.7, 36.9, 31.5, 26.6 (2C), 22.5, 13.9; ms: m/z 205 (M^+-C_5H_{11}). Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.21; H, 7.25; N, 10.14. Found: 65.34; 7.29; N, 10.06.

1-(3-Isopropoxypropyl)-6-nitro-4(1*H*)-quinolinone (10d). This compound (88 mg, 75%) was isolated as a yellow oil. IR: 1687, 1516, 1317 cm^{-1}; ^{1}H NMR: δ 8.70 (d, 1H, J = 2.7), 8.14 (dd, 1H, J = 9.4, 2.7), 6.84 (d, 1H, J = 9.4), 3.71 (t, 2H, J = 7.0), 3.63 (t, 2H, J = 7.1), 3.57 (septet, 1H, J = 6.1), 3.50 (t, 2H, J = 6.0), 2.75 (t, 2H, J = 7.0), 1.92 (quintet, 2H, J = 7.0), 1.18 (d, 6H, J = 6.1); ^{13}C NMR: δ 191.4, 154.3, 137.4, 129.8, 125.2, 117.7, 112.9, 71.8, 64.4, 48.9, 48.5, 36.9, 27.4, 22.0 (2C); ms: m/z 205 (M^+-$C_5H_{11}O$). Anal. Calcd. for $C_{15}H_{20}N_2O_4$; C, 61.64; H, 6.85; N, 9.59. Found: C, 61.76; H, 6.89; N, 9.53.

1-Isobutyl-6-nitro-4(1*H*)-quinolinone (10e). This compound (72 mg, 72%) was isolated as a yellow solid, mp 102–104°C. IR: 1686, 1520, 1315 cm^{-1}; ^{1}H NMR: δ 8.73 (d, 1H, J = 2.7), 8.14 (dd, 1H, J = 9.4, 2.7), 6.71 (d, 1H, J = 9.4), 3.71 (t, 2H, J = 7.0), 3.28 (d, 2H, J = 7.4), 2.76 (t, 2H, J = 7.0), 2.13 (nonet, 1H, J = 6.6), 1.04 (d, 6H, J = 6.6); ^{13}C NMR: δ 191.3, 154.4, 137.3, 129.8, 125.3, 117.6, 112.7, 59.6, 49.5, 36.8, 27.4, 20.3, 20.2; ms: m/z 205 (M^+-C_3H_7). Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.90; H, 6.45; N, 11.29. Found: C, 62.94; H, 6.45; N, 11.26.

1-Cyclohexyl-6-nitro-4(1*H*)-quinolinone (10f). This compound (84 mg, 77%) was isolated as a yellow solid, mp 174–177°C. IR: 1688, 1504, 1316 cm^{-1}; ^{1}H NMR: δ 8.77 (d, 1H J = 2.5), 8.16 (dd, 1H, J = 9.5, 2.5), 6.86 (d, 1H, J = 9.5), 3.81 (tt, 1H, J = 11.5, 3.3), 3.60 (d, 2H, J = 7.0), 2.70 (d, 2H, J = 7.0), 1.91 (m, 4H), 1.78 (m, 1H), 1.58 (m, 2H), 1.45 (m, 2H), 1.21 (m, 1H); ^{13}C NMR: δ 191.6, 154.3, 137.4, 129.9, 12.57, 118.5, 112.6, 57.4, 41.2, 37.3, 30.0 (2C), 25.8 (2C), 25.4; ms: m/z 274 (M^+). Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.69; H, 6.57; N, 10.22. Found: C, 65.70; H, 6.56; N, 10.20.

1-*tert*-Butyl-6-nitro-4(1*H*)-quinolinone (10g). This compound (70 mg, 71%) was isolated as a yellow solid, mp 132–134°C. IR: 1688, 1499, 1317 cm^{-1}; ^{1}H NMR: δ 8.81 (d, 1H, J = 2.9), 8.13 (dd, 1H, J = 9.6, 2.9), 7.19 (d, 1H, 9.6), 3.73 (t, 2H, J = 6.6), 2.70 (t, 2H, J = 6.6), 1.61 (s, 9H); ^{13}C NMR: δ 192.5, 155.2, 137.9, 127.9, 125.5, 121.2, 117.5, 57.7, 44.2, 38.9, 29.6 (3C); ms: m/z 233 (M^+-CH_3). Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.90; H, 6.45; N, 11.29. Found: C, 62.93; H, 6.44; N, 11.27.

6-Nitro-1-phenyl-4(1*H*)-quinolinone (10h). This compound (77 mg, 72%) was isolated as a yellow solid, mp 126–128°C. IR: 1688, 1498, 1314 cm^{-1}; ^{1}H NMR: δ 8.80 (d, 1H, J = 2.7), 8.00 (dd, 1H, J = 9.4, 2.7), 7.54 (t, 2H, J = 7.5), 7.41 (t, 1H, J = 7.4), 7.30 (d, 2H, J = 7.4), 6.59 (d, 1H, J = 9.4), 4.03 (t, 2H, J = 6.9), 2.93 (t, 2H, J = 7.0); ^{13}C NMR: δ 191.1, 154.5, 144.0, 138.9, 130.5, 129.3, 127.9, 126.1, 125.0,

118.4, 115.4, 50.6, 37.4; ms: *m*/*z* 268 (M^+). Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.48; N, 10.45. Found: C, 67.18; H, 4.47; N, 10.42.

Representative procedure for the tandem Michael-S_NAr reaction using 8: 1-Benzyl-4(1*H*)-quinolinone (11a). This reaction was run using 75 mg (0.50 mmoles) of **8** and the general procedure given above for the preparation of **10a**. This compound (72 mg, 61%) was isolated as a light yellow solid, mp 111–114°C [16]. IR: 1673 cm^{-1}; ^1H NMR δ 7.93 (dd, 1H, *J* = 7.8, 1.8), 7.39–7.24 (complex, 6H), 6.72 (t, 1H, *J* = 8.0), 6.70 (d, 1H, *J* = 8.4), 4.57 (s, 2H), 3.60 (t, 2H, *J* = 7.0), 2.75 (t, 2H, *J* = 7.0); ^{13}C NMR: δ 193.5, 151.7, 137.2, 135.5, 128.8, 128.2, 127.4, 126.7, 119.8, 117.0, 113.4, 55.2, 49.4, 38.0; ms: *m*/*z* 146 (M^+-C_7H_7). Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.91. Found: C, 80.97; H, 6.35; N, 5.89.

1-(2-Phenylethyl)-4(1*H*)-quinolinone (11b). This compound (73 mg, 58%) was isolated as a yellow oil. IR: 1673 cm^{-1}; ^1H NMR δ 7.91 (dd, 1H, *J* = 7.8, 1.8), 7.39 (ddd, 1H, *J* = 8.6, 7.2, 1.8), 7.36–7.18 (complex, 5H), 6.78 (d, 1H, *J* = 8.6), 6.71 (t, 1H, *J* = 7.2), 3.61 (t, 2H, *J* = 7.5), 3.41 (t, 2H, *J* = 7.0), 2.91 (t, 2H, *J* = 7.5), 2.59 (t, 2H, *J* = 7.0); ^{13}C NMR: δ 193.5, 150.8, 138.9, 135.4, 128.7, 128.6, 128.4, 126.5, 119.6, 116.4, 112.7, 53.3, 49.4, 37.7, 32.7; ms: *m*/*z* 160 (M^+-C_7H_7). Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.27; H, 6.77; N, 5.58. Found: C, 81.21; H, 6.74; N, 5.62.

1-Hexyl-4(1*H*)-quinolinone (11c). This compound (90 mg, 78%) was isolated as a yellow oil. IR: 1677 cm^{-1}; ^1H NMR: δ 7.89 (dd, 1H, *J* = 7.8, 1.8), 7.35 (ddd, 1H, *J* = 8.6, 7.0, 1.8), 6.70 (d, 1H, *J* = 8.6), 6.67 (t, 1H, *J* = 7.8), 3.51 (t, 2H, *J* = 7.0), 3.34 (t, 2H, *J* = 7.6), 2.68 (t, 2H, *J* = 7.0), 1.61 (quintet, 2H, *J* = 7.6), 1.34 (m, 6H), 0.90 (distorted t, 3H, J = 6.8); ^{13}C NMR: δ 193.5, 151.4, 135.3, 128.3, 119.5, 116.1, 112.8, 51.5, 49.0, 37.8, 31.6, 26.8, 26.1, 22.6, 14.0; ms: *m*/*z* 160 (M^+-C_5H_{11}). Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.92; H, 9.09; N, 6.06. Found: C, 77.81; H, 9.04; N, 6.12.

1-(3-Isopropoxypropyl)-4(1*H*)-quinolinone (11d). This compound (86 mg, 70%) was isolated as a yellow oil. IR: 1674 cm^{-1}; ^1H NMR: δ 7.89 (dd, 1H, *J* = 7.8, 1.8), 7.35 (ddd, 1H, *J* = 8.5, 7.0, 1.8), 6.78 (d, 1H, *J* = 8.5), 6.67 (ddd, 1H, *J* = 7.8, 7.0, 1.8), 3.61–3.45 (complex, 7H), 2.68 (t, 2H, *J* = 7.0), 1.86 (quintet, 2H, *J* = 6.1), 1.17 (d, 6H, *J* = 6.1); ^{13}C NMR: δ 193.5, 151.4, 135.3, 128.2, 119.5, 116.2, 113.0, 71.6, 65.0, 49.1, 48.4, 37.8, 27.2, 22.1 (2C); ms: *m*/*z* 160 (M^+-$C_5H_{11}O$). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 72.96; H, 8.54; N, 5.64.

1-Isobutyl-4(1*H*)-quinolinone (11e). This compound (76 mg, 75%) was isolated as a yellow oil. IR: 1677 cm^{-1}; ^1H NMR δ 7.89 (dd, 1H, *J* = 7.8, 1.8), 7.34 (ddd, 1H, *J* = 8.6, 7.0, 1.8), 6.68 (d, 1H, *J* = 8.8), 6.67 (t, 1H, *J* = 7.8), 3.54 (t, 2H, *J* = 7.0), 3.10 (d, 2H, *J* = 7.4), 2.68 (t, 2H, *J* = 7.0), 2.07 (nonet 1H, *J* = 6.8), 1.01 (d, 6H, *J* = 6.6); ^{13}C NMR: δ 193.5, 151.7, 135.3, 128.3, 119.2, 116.0, 112.7, 59.6, 50.0, 37.8, 27.4, 20.4 (2C); ms: *m*/*z* 160 (M^+-C_3H_7). Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.85; H, 8.37; N, 6.90. Found: C, 76.90; H, 8.40; N, 6.83.

1-Cyclohexyl-4(1*H*)-quinolinone (11f). This compound (62 mg, 54%) was isolated as a yellow oil. IR: 1674 cm^{-1}; ^1H NMR δ 7.92 (dd, 1H, *J* = 7.8, 1.8), 7.35 (ddd, 1H, *J* = 8.6, 7.0, 1.8), 6.83 (d, 1H, *J* = 8.8), 6.67 (t, 1H, *J* = 7.8), 3.68 (tt, 1H, *J* = 11.1, 3.1), 3.43 (t, 2H, *J* = 7.0), 2.62 (t, 2H, *J* = 7.0), 1.85 (m, 4H), 1.74 (m, 1H), 1.45 (m, 4H), 1.15 (m, 1H); ^{13}C NMR: δ 193.9, 151.6, 135.3, 128.6, 120.1, 116.1, 112.7, 56.0, 41.5, 38.3, 29.8 (2C), 26.1 (2C), 25.7; ms: *m*/*z* 229 (M^+). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.60; H, 8.30; N, 6.11. Found: C, 78.54; H, 8.34; N, 6.04.

3-(*tert*-Butylamino)-1-(2-fluorophenyl)-1-propanone (12a). This compound (58 mg, 52%) from *tert*-butylamine and **8** was isolated as a yellow oil. To prevent extraction of the product into the aqueous layer during workup, the reaction was diluted with water and made slightly basic with 0.1*M* NaOH before extraction with ether. Attempts to purify this material by chromatography resulted in extensive decomposition, and thus, characterization was carried out on the crude product. IR: 3454, 1685, 1269 cm^{-1}; ^1H NMR: δ 7.87 (td, 1H, *J* = 7.6, 1.8), 7.50 (m, 1H), 7.22 (t, 1H, *J* = 7.8), 7.12 (dd, 1H, *J* = 11.2, 8.0), 3.20 (td, 2H, *J* = 6.2, 3.3), 2.96 (t, 2H, *J* = 6.2), 1.71 (br s, 1H), 1.13 (s, 9H); ^{13}C NMR: δ 198.1, 162.0 (d, *J* = 254.7), 134.5 (d, *J* = 8.8), 130.5 (d, *J* = 2.9), 130.4, 124.4 (d, *J* = 3.4), 116.7 (d, *J* = 24.2), 50.5, 44.7 (d, *J* = 7.4), 37.3 (d, *J* = 2.2), 28.9 (3C); ms: *m*/*z* 123 (M^+-$C_6H_{14}N$).

1-(2-Fluorophenyl)-3-(phenylamino)-1-propanone (12b). This compound (79 mg, 65%) from aniline and **8** was isolated as a yellow solid, mp 69–71°C. IR: 3405, 1683, 1264 cm^{-1}; ^1H NMR: δ 7.88 (td, 1H, *J* =7.8, 1.8), 7.50 (m, 1H), 7.25–7.08 (complex, 5H), 6.70 (t, 1H, *J* = 7.2), 6.64 (dd, 1H, *J* = 7.6, 1.0), 4.09 (br s, 1H), 3.58 (t, 2H, *J* = 6.1), 3.28 (m, 2H); ^{13}C NMR: δ 197.4, 162.1 (d, *J* = 254.7), 147.7, 134.8 (d, *J* = 8.8), 130.5 (d, *J* = 2.2), 129.3, 124.5 (d, *J* = 3.7), 117.5, 116.8, 116.6 (d, *J* = 11.8), 112.9, 42.8, 38.5; ms: *m*/*z* 123 (M^+-$C_8H_{10}N$). Anal. Calcd. for $C_{15}H_{14}FNO$: C, 74.07; H, 5.76; N, 5.76. Found: C, 73.98; H, 5.79; N, 5.70.

Representative procedure for the tandem Michael-S_NAr reaction using 9: 1-(2-Fluoro-5-methoxyphenyl)-3-(benzylamino)-1-propanone (13) and (±)-(3*S,4*R**)-1-benzyl-3-(2-fluoro-5-methoxybenzoyl)-4-(2-fluoro-5-methoxyphenyl)-4-piperidinol (15).** This reaction was run using 75 mg (0.42 mmoles) of **9** and the general procedure given above for the preparation of **10a**. The reaction did not yield the dihydroquinolinone but yielded only products resulting from the initial conjugate addition without subsequent S_NAr ring closure. The 1:1 Michael addition product **13** (14 mg, 12%) was isolated as a yellow oil. IR: 3333, 2815, 1685, 1271 cm^{-1}; ^1H NMR: δ 7.32 (m, 5H), 7.25 (m, 1H), 7.04 (m, 2H), 3.83 (s, 2H), 3.81 (s, 3H), 3.22 (td, 2H, *J* = 6.2, 3.3), 3.02 (t, 2H, *J* = 6.2), 1.77 (br s, 1H); ^{13}C NMR: δ 197.7 (d, *J* = 4.4), 156.6 (d, *J* = 247.4), 155.7, 140.2, 128.4, 128.1, 126.9, 125.5 (d, *J* = 14.7), 121.5 (d, *J* = 8.8), 117.7 (d, *J* = 26.5), 112.7 (d, *J* = 2.9), 55.9, 54.0, 43.9, 43.8 (d, *J* = 7.4); ms: *m*/*z* 153 (M^+-$C_9H_{12}N$). Anal. Calcd. for $C_{17}H_{18}FNO_2$: C, 71.08; H, 6.27; N, 4.88. Found: C, 71.12; H, 6.29; N, 4.82.

This reaction also yielded piperidinol **15**, which results from the silica gel-promoted aldol ring closure of the 2:1 Michael addition product **14**. Compound **15** (82 mg, 42%) was isolated as a viscous yellow oil. IR: 3462, 2830, 1663 cm^{-1}; ^1H NMR: δ 7.39 (d, 2H, *J* = 7.4), 7.32 (t, 2H, *J* = 7.4), 7.25 (m, 2H), 6.97 (m, 2H), 6.91 (m, 1H), 6.77 (dd, 1H, *J* = 11.5, 8.9), 6.63 (dt, 1H, *J* = 8.9, 3.5), 4.89 (d, 1H, *J* = 2.3), 4.71 (dd, 1H, *J* = 11.1, 3.5), 3.76 (s, 3H), 3.69 (s, 3H), 3.68 (s, 2H), 3.03 (dd, 1H, *J* = 11.1, 3.5), 2.75 (complex, 3H), 2.72 (m, 1H), 1.65 (d, 1H, *J* = 13.7); ^{13}C NMR: δ 203.2 (d, *J* = 3.7), 156.1 (d, *J* = 250.3), 155.6, 155.5, 153.2 (d, *J* = 237.8), 138.3, 134.1 (d, *J*

= 14.0), 128.8, 128.2, 127.0, 125.3 (d, J = 13.9), 121.9 (d, J = 8.8), 117.7 (d, J = 25.8), 116.6 (d, J = 26.5), 113.9 (d, J = 8.8), 112.9 (d, J = 4.4), 112.6 (d, J = 2.2), 72.3 (d, J = 5.9), 62.0, 55.7, 55.6, 53.1 (t, J = 7.4), 51.4, 48.5, 36.2 (d, J = 2.9); ms (30 eV): m/z 467 (M^+). Anal. Calcd for $C_{27}H_{27}F_2NO_4$: C, 69.38; H, 5.78; N, 3.00. Found: C, 69.44; H, 5.81; N, 2.93. The ^1H and ^{13}C NMR spectra compare well with calculated spectra [12], but the stereochemical assignment is tentative.

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