A Convenient Preparation of *N*-Acyl-1-aza-1,3-diene from *β*-Formylenamide and Its Utility in Inverse Electron Demand Diels−Alder Reactions

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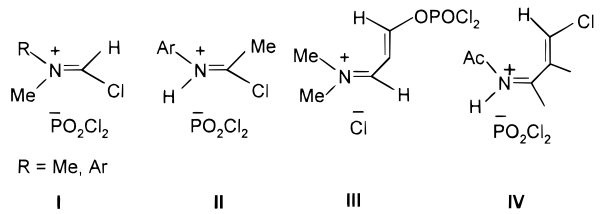
Indroduction

The Diels−Alder reaction of 1-azadienes is a valuable methodology for synthesis of nitrogen heterocycles[1] bearing endocyclic enamine moieties that are key intermediates in the preparation of complicated heterocycles[2a] and natural products.[2b] The 4π participation of simple 1-azadienes is rarely observed in normal [4 + 2] cycloaddition reactions; however, this problem could be circumvented by introducing either electron-withdrawing[1,3] or electron-donating[4] substitutents onto the nitrogen. Fowler[2] and Boger[5] have shown that substitution of the azadiene nitrogen by a strongly electron-withdrawing *N*-acyl or *N*-sulfonyl group favors considerably the inverse electron demand Diels−Alder(IEDDA) reactivity of the desired azadienes. Nevertheless, enormous efforts have been made toward production of electron-deficient 1-aza-1,3-butadienes that enable 4π participation of α,β-unsaturated imines in [4 + 2] cycloaddition reactions. These have included intramolecular [4 + 2] cycloaddition of in situ generated *N*-acyl-1-aza-1,3-butadienes by vacuum pyrolysis[6] and under thermal condition,[7] in situ generated *o*-quinomethide monoimines,[8] the $HOMO_{diene}$ controlled Diels−Alder reaction of 1-(dimethylamino)-1-aza-1,3-butadienes,[9] the Lewis acid catalyzed intramolecular [4 + 2] cycloaddition reaction of in situ generated 2[(*tert*-butyldimethylsilyl)oxy]-1-aza-1,3-butadienes,[10] and intermolecular [4 + 2] cycloaddition of *N*-sulfonyl-1-aza-1,3-butadienes.[11] Recently significant attention has been drawn[12] to the influence of a cyano group at C-2, together with different nitrogen substituents (COR, Ph, alkyl, OMe, SO_2Ph), on the Diels−Alder reactivity of azadiene systems. Interestingly, literature reveals that C-2-alkyl substituted *N*-acyl-1-azadienes are rare compounds, although corresponding 2-alkyl-*N*-sulfonyl-1-azadienes have provided well-behaved dienophiles for [4 + 2] cycloaddition studies.[13]

Scheme 1



The Vilsmeier reagent, which is derived from *N*,*N*-dimethylformamide and phosphorus oxychloride, corresponds to a chloromethyleneiminium salt structure (**I**, R=Me, Scheme 1). The potential of carbon−carbon bond-forming reactions of halomethylene iminium salts involving aromatic and acyclic or alicyclic nuclei has been extensively studied.[14] The Vilsmeier reactions of enamides were found to proceed by cyclization of intermediate **II** to give fused pyridoderivatives.[15] The ring closure of *N*-aryl-*N*-methylformamides to quinolines can also be effected by treatment of electrophilic iminium salt (**I**, R = Ar) with enamine via "reverse Vilsmeier approach".[16] All of these examples include amine precursors in which an enolizable formyl or acyl group is directly linked to the nitrogen atom. Nevertheless, Ulrich et al.[17] reported that 3-(dimethylamino)-acrolein is a prototype vinyl homologue of dimethylformamide, which could be employed for preparation of α,β-unsaturated imine **III** to incorporate an acrolein moiety to a suitable nucleophile. These results suggested that if properly substituted

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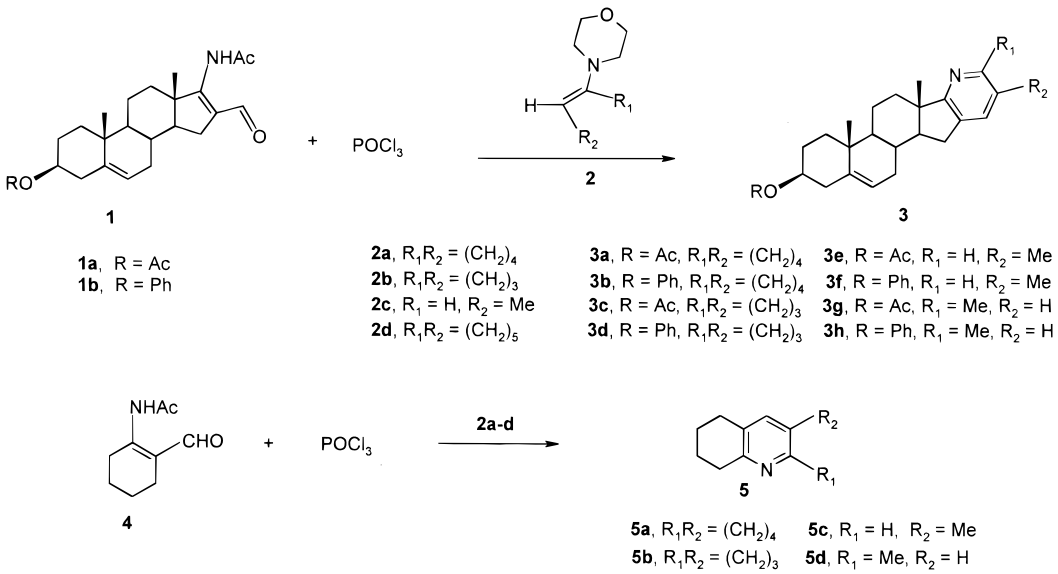
Scheme 2



enamines or enamides were chosen, a similar enolization sequence would yield a 1-aza-1,3-diene system.

With this in mind, we elected to synthesize a novel class of α,β-unsaturated imines of the type **IV** from 1-acetamido-2-formyl-1-alkenes. It was anticipated that reaction of this β-formylenamide and $POCl_3$ would generate a highly reactive and electrophilic substrate that could behave as an electron-deficient 1-aza-1,3-diene in a [4 + 2] cycloaddition reaction. Recently we have reported the preparation of a novel class of steroidal β-formylenamide[18] and conveniently employed it as potential intermediate for synthesis of 17,17-dichloro-16-(*E*)-chloromethyleneandrost-5-enes[19a] and steroidal des-D diynes.[19b] We foresee enormous scope for this functionality as a new substrate in the emerging field of enamides.[20] Herein, we report a facile $POCl_3$-mediated conversion of β-formylenamides to *N*-acyl-1-aza-1,3-diene systems and their convenient application in an IEDDA reaction with enamines[21] to construct ring-D annelated pyrido(17,16-b)- and tetrahydroquinolino(17,16-b)steroids.[22]

Results and Discussion

Steroidal β-formyl enamides (**1a,b**) were prepared from 16-dehydropregnenolone oxime under the influence of Vilsmeier reagent in good yields.[18] Conversion of cyclohexanone to 1-acetamido-1-cyclohexene[23] followed by Vilsmeier formylation under mild condition afforded 1-acetamido-2-formyl-1-cyclohexene (**4**) in 69% yield. Treatment of **1a** with 3 molar equiv of $POCl_3$ at 0−10 °C for 1 h and subsequent reaction with freshly prepared *N*-morpholino-1-cyclohexene (**2a**) in refluxing dichloroethane gave **3a** in 51% yield (Scheme 2). In addition, from the reaction mixture the compound 3-β-acetoxy-17-oxo-16(*E*)-chloromethylene-androst-5-ene[19a] was isolated in 30% yield. Similarly, steroidal formyl enamides (**1a,b**) in combination with $POCl_3$ reacted with morpholino-enamines (**2a**−**c**) to afford products **3a**−**f** in 51−57% yields. However, the reaction of *N*-morpholino-1-propene (**2c**) with **1a** resulted 3β-acetoxy-5′,6′-dihydro-5′-methyl-6′-morpholino-pyrido(17,16-b)androst-5-ene (**D**, R_1 = H, R_2 = Me),[24] which required additional acid treatment to give product **3e**. Similarly, the alicylic formyl enamide (**4**) reacted with enamines (**2a**−**c**) to afford **5a**−**c** in 47−52% yields. All of the products were characterized by spectroscopical and elemental analysis.

The reaction is proposed to proceed by an IEDDA reaction mechanism involving a transient *N*-acyl-1-aza-1,3-butadiene intermediate (**A**). The $POCl_3$-promoted azadiene intermediate might form as a result of enolization and chlorination of β-formyl enamides (**1a**), followed by abstraction of the proton from quaternary nitrogen by $^{-}OPOCl_2$ species. The *N*-acyl-1-azadiene moiety acts as an electron-deficient diene and is involved in an IEDDA reaction[21] with an electron-rich enamine (**2a**) to afford an endocyclic piperidine enamine intermediate [**B**, $R_1R_2 = (CH_2)_4$], which facilitates loss of Cl^- ion to form iminium intermediate **C**. The nucleophilic attack on the *N*-carbonyl group leads to loss of AcNu, which is followed by elimination of morpholine to afford aromatic product **3a** (Scheme 3). The ^{1}HNMR spectra of intermediate **A** exhibited a singlet signal at δ 7.18 for conjugated C-16 imine proton, thus favoring an azadiene structure. All

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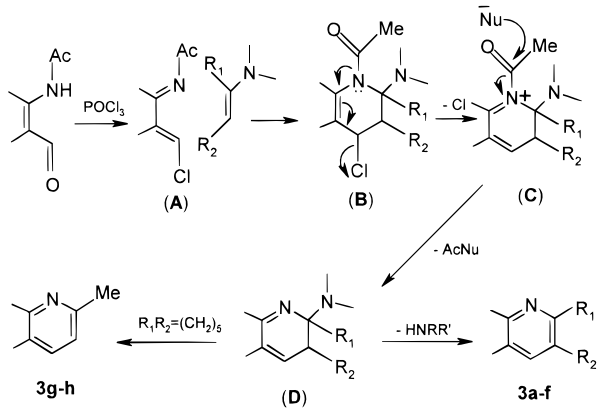
Scheme 3



attempts to isolate intermediate **A** failed; rather we obtained 3-β-acetoxy-17-oxo-16(*E*)-chloromethylene-androst-5-ene as the sole product, which further supported the existence of a 1-azadiene intermediate.[19a] The isolation of stable intermediate **D** (R_1 = H, R_2 = Me) from reaction between **1a** and aliphatic enamine (**2c**) indicated that conformationally less strained cycloadduct **D** disfavored the loss of morpholine to aromatize under reaction conditions.

In contrast, the reaction of *N*-morpholino-1-cyclohepten (**2d**) with *N*-acyl-1-azadiene of **1a,b** afforded **3g,h** instead of the expected cycloheptane-fused pyridosteroid [**3**, R = Ac or PhCO, $R_1R_2 = (CH_2)_5$]. The ^{1}H NMR of **3g** showed two characteristic ortho-coupled signals at δ 7.42 and 6.19 (J = 7 Hz) for the pyridine ring. Obviously, the formation of **3g** resulted from the cleavage of the cycloheptane ring in the cycloadduct (**D**). The formation of the unexpected reaction product **3g**, therefore, may be accounted for by an unusual type of bond breakage and rearrangement under thermal condition leading to aromatization of dihydropyridine intermediate **D** [$R_1R_2 = (CH_2)_5$] with concommital loss of morpholine and butadiene. The generation of butadiene was ascertained by GLC analysis of the gaseous product. Similarly, formyl enamide **4** reacted with **2d** to afford **5d** in 45% yield.

To increase the electron-deficient character[25] of *N*-acyl conjugated imines, the catalytic effect of a Lewis acid[26] on the course of the IEDDA reaction was studied. The $TiCl_4$-catalyzed reaction of **1a** with enamine **2a** showed enhancement of the electrophilicity of 1-azadiene and gave **3a** as a single regioisomer (82%). Similarly, $BF_3{\cdot}OEt_2$ was found to stabilize intermediate **A** and catalyzed the [4 + 2] cycloaddition reaction, minimizing side products (Table 1). The mechanism of the reaction is not clear; however, it may be assumed that the Lewis acid probably forms a complex with the oxygen atom of the acetyl group, enhancing the electron-deficient character of *N*-acyl-1-azadiene and accelerating the rate of [4 + 2] cycloaddition reaction.

The work represents our first attempt to use β-formylenamides as useful precursors of 1-aza-1,3-butadiene in carbocycles. The route presented here should be useful in the synthesis of a variety of other pyridine and quinoline derivatives. From our study it is evident that Lewis acid catalyses the intermolecular IEDDA reaction of *N*-acyl-1-azadiene and enamine. From the standpoints of yield and experimental simplicity, the $POCl_3$-mediated process represents an attractive strategy to hitherto inaccessible 2-alkyl substituted *N*-acyl-1-aza-1,3-butadienes. Currently we are studying the scope of this reaction in regard to other electron-rich dienophiles.

Table 1. Influence of Lewis Acid on Inverse Electron Demand Diels–Alder Reactions

entry	β-formyl enamide[a]	enamine	Lewis acid[b]	reaction time/temp	prod.[c]	yield (%)[d]
1	**1a**	**2a**		4 h, 80	**3a**	51
2			$TiCl_4$	1 h, 20 °C	**3a**	82
3	**1b**	**2a**		4 h, 80 °C	**3b**	55
4			$TiCl_4$	1 h, 20 °C	**3b**	85
5	**1a**	**2b**		4 h, 80 °C	**3c**	57
6			$TiCl_4$	1 h, 20 °C	**3c**	88
7	**1b**	**2b**		4 h, 80 °C	**3d**	52
8			$TiCl_4$	1 h, 20 °C	**3d**	80
9	**1a**	**2c**		5 h, 80 °C	**3e**	57
10			$BF_3{\cdot}OEt_2$	2 h, 20 °C	**3e**	74
11	**1b**	**2c**		5 h, 80 °C	**3f**	51
12			$BF_3{\cdot}OEt_2$	2 h, 20 °C	**3f**	72
13	**1a**	**2d**		4.5 h, 80 °C	**3g**	55
14			$BF_3{\cdot}OEt_2$	1.5 h, 20 °C	**3g**	75
15	**1b**	**2d**		5.5 h, 80 °C	**3h**	53
16			$BF_3{\cdot}OEt_2$	2 h, 20 °C	**3h**	69

[a] Three molar equivalents of $POCl_3$ was employed. [b] One-half molar equivalent of Lewis acid was used. [c] All reactions were carried under nitrogen atmosphere. [d] Isolated yields.

Experimental Section

All anhydrous reactions were performed under a nitrogen atmosphere using flame-dried glassware. DMF was dried over CaH_2, and $POCl_3$ was freshly distilled. Compounds **1a,b** were prepared from 16-DPA oxime following our earlier procedure.[18]

1-Acetamido-2-formyl-1-cyclohexene (4). A mixture of acetamide (300 mg, 5 mmol), cyclohexanone (980 mg, 10 mmol), and *p*-toluenesulfonic acid (50 mg) was placed in a 250 mL round-bottom flask containing 100 mL of dry toluene and refluxed under Dean stark conditions for 24 h. After removal of a calculated amount of water, the reaction was stopped and the solvent was distilled under reduced pressure to obtain a thick solid mass. It was extracted with hexane/CH_2Cl_2 and dried over Na_2SO_4, and solvent was removed to afford 1-acetamido-1-cyclohexene, yield 514 mg (74%), mp 59–61 °C (lit.[23] 62–64 °C). The solid product was dissolved in CH_2Cl_2 (50 mL), cooled, and added to a Vilsmeier reagent freshly prepared from $POCl_3$ (5.84 mL) and DMF (5.60 mL). The reaction was stirred at 0–15 °C for 3 h and worked up by quenching in ice-cold water. The organic layer was separated after neutralization with $NaHCO_3$, and the aqueous portion was extracted with CH_2Cl_2. The organic portions were combined, washed with water, and dried over Na_2SO_4. Removal of the solvent and column chromatography separation (toluene/acetone 90:10) gave **4** as a white solid: yield 426 mg (69%), mp 115–16 °C (ethyl acetate), R_f = 0.15 ($CHCl_3$); IR ν_{max} (KBr) 3250, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.06 (bs, 1H, –NH), 9.28 (s, 1H, CHO), 3.07 (s, 2H), 2.42 (s, 2H), 2.13 (s, 3H), 1.93 (bs, 4H); MS m/z 167 (M^+). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.64; H, 7.83; N, 8.37. Found: C, 64.69; H, 7.73, N, 8.52.

3β-Acetoxy-(5′,6′,7′,8′-tetrahydro)-quinolino(17,16-b)androst-5-ene (3a). Powdered 16-formyl-17-acetamido-androst-5,16-diene (**1a**, 399 mg, 1 mmol) was added to $POCl_3$ (459 mg, 3 mmol) under a nitrogen atmosphere at 0 °C in a 250 mL round-bottom flask. The reaction mixture was stirred magnetically at 0 °C for 15 min, during which time it turned from colorless to red. It was diluted with dry $ClCH_2CH_2Cl$ (100 mL), and to this cold mixture was added the morpholine enamine of cyclohexanone (**2a**, 451 mg, 3 mmol). The reaction mixture was allowed to stir for 30 min at room temperature to increase the reaction temperature to 25 °C, and then it was further refluxed for 4 h

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under a nitrogen atmosphere. The reaction was monitored by TLC, and on completion of reaction it was quenched in ice-cold water. After neutralization with solid $NaHCO_3$ to pH ~7.5, the organic layer was separated, and the aqueous layer was extracted with $ClCH_2CH_2Cl$. The organic extracts were combined, washed with water, and dried over Na_2SO_4. Removal of the solvent gave a red gummy product that was purified by prepapative TLC on silica gel (EtOAc/hexane 20:80) to afford product **3a** as white solid: yield 215 mg (51%), mp 173 °C (methanol), $[\alpha]^{25}_D$ −33° (*c*, 0.7, $CHCl_3$), R_f = 0.6 (hexane/EtOAc 80:20); IR ν_{max} (KBr) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (s,1H), 5.41 (bs, 1H), 4.61 (m,1H), 2.89 (bs, 2H), 2.70−2.61 (m, 3H), 2.43−2.29 (m, 6H), 2.03 (s, 3H), 1.10 (s, 3H), 0.97 (s, 3H), 1.91−1.13 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 171.55, 170.85, 162.52, 140.66, 134.54, 134.13, 131.04, 119.66, 74.73, 56.03, 50.68, 44.80, 38.74, 36.92, 36.92, 34.31, 31.14, 30.86, 30.20, 29.92, 28.60, 23.50, 22.12, 21.56, 20.17, 19.74, 19.26, 17.17; MS *m*/*z* 359 ($M^+ - CH_3COOH$), 344. Anal. Calcd for $C_{28}H_{37}NO_2$: C, 80.14; H, 8.88; N, 3.33. Found: C, 79.98; H, 8.76, N, 3.52.

3β-Benzoyloxy-(5′,6′,7′,8′-tetrahydro)-quinolino(17,16-b)-androst-5-ene (3b): 265 mg (55%), mp 170 °C (Et_2O/ *n*-hexane 50:50) $[\alpha]^{25}_D$ −9.5° (*c*, 0.70, $CHCl_3$), R_f = 0.7 (*n*-hexane/EtOAc 90:10). Anal. Calcd for $C_{33}H_{39}NO_2$: C, 82.29; H, 8.16; N, 2.91. Found: C, 82.15; H, 8.22, N, 3.01.

3β-Acetoxy-(5′,6′-trimethylene)-pyrido(17,16-b)androst-5-ene (3c): 230 mg (57%), mp 176 °C (methanol), $[\alpha]^{25}_D$ −34.2° (*c*, 1.95, $CHCl_3$), R_f = 0.6 ($CHCl_3$/EtOAc 94:6). Anal. Calcd for $C_{27}H_{35}NO_2$: C, 79.96; H, 8.69; N, 3.45. Found: C, 80.10; H, 8.85, N, 3.56.

3β-Benzoyloxy-(5′,6′-trimethylene)-pyrido(17,16-b)-androst-5-ene (3d): 244 mg (52%), mp 177 °C (Et_2O/*n*-hexane 50:50), $[\alpha]^{25}_D$ −8° (*c*, 1.05, $CHCl_3$), R_f = 0.65 (*n*-hexane/EtOAc 75:25). Anal. Calcd for $C_{32}H_{37}NO_2$: C, 82.19; H, 7.98; N, 2.99. Found: C, 82.25; H, 7.72, N, 3.08.

3β-Acetoxy-(5′-methyl)-pyrido(17,16-b)androst-5-ene (3e): 215 mg (57%), mp 186 °C (methanol) $[\alpha]^{25}_D$ −50° (*c*, 0.25, $CHCl_3$), R_f = 0.6 (*n*-hexane/EtOAc 80:20). Anal. Calcd for $C_{25}H_{33}NO_2$: C, 79.11; H, 8.76; N, 3.69. Found: C, 79.28; H, 8.56, N, 3.50.

3β-Benzoyloxy-5′-methyl-pyrido(17,16-b)androst-5-ene (3f): 226 mg (51%), mp 190 °C (methanol), $[\alpha]^{25}_D$ −15° (*c*, 0.90, $CHCl_3$), R_f = 0.70 (*n*-hexane/EtOAc 80:20). Anal. Calcd for $C_{30}H_{35}NO_2$: C, 81.59; H, 7.99; N, 3.17. Found: C, 81.45; H, 7.89, N, 3.11.

3β-Acetoxy-(6′-methyl)-pyrido(17,16-b)androst-5-ene (3g): 210 mg (55%), mp 210 °C (*n*-hexane/CH_2Cl_2 80:20) $[\alpha]^{25}_D$ −45.2° (*c*, 0.75, $CHCl_3$), R_f = 0.6 (*n*-hexane/EtOAc 80:20). Anal. Calcd for $C_{25}H_{33}NO_2$: C, 79.11; H, 8.76; N, 3.69. Found: C, 79.58; H, 8.36, N, 3.59.

3β-Benzoyloxy-6′-methyl-pyrido(17,16-b)androst-5-ene (3h): 235 mg (53%), mp 215 °C (methanol), $[\alpha]^{25}_D$ −12° (*c*, 1, $CHCl_3$), R_f = 0.70 (*n*-hexane/EtOAc 80:20). Anal. Calcd for $C_{30}H_{35}NO_2$: C, 81.59; H, 7.99; N, 3.17. Found: C, 81.50; H, 7.88, N, 3.10.

1,2,3,4,5,6,7,8-Octahydroacridine (5a): yield 95 mg (51%), mp 69 °C (lit.[27] 70−71 °C), R_f = 0.8 (toluene/CH_2Cl_2 80:20); IR ν_{max} (KBr) 2950, 1520 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.09 (s, 1H), 3.10−2.65 (m, 8H), 1.80−1.52 (m, 8H); MS *m*/*z* 187 (M^+).

2′,3′-Trimethylene-5,6,7,8-tetrahydroquinoline (5b): 82 mg (47%), $bp_{18\ mmHg}$160−61 °C (lit.[28] $bp_{12\ mmHg}$140−42 °C), R_f = 0.8 (toluene); IR ν_{max} (KBr) 2930, 1525, cm^{-1}, ^1H NMR ($CDCl_3$) δ 6.90 (s, 1H), 3.15−2.60 (m, 8H), 2.05−1.85 (m, 6H); MS *m*/*z* 173 (M^+).

3-Methyl-5,6,7,8-tetrahydroquinoline (5c): 76 mg (52%), $bp_{20\ mmHg}$ 135−36 °C (lit.[27] $bp_{17\ mmHg}$ 126−27 °C), R_f = 0.75 (toluene), IR ν_{max} (KBr) 2900, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (d, 1H, *J* = 2.5), 7.25 (d, 1H, *J* = 2.5), 2.90−2.75 (m, 4H), 2.30 (s, 3H), 1.95−1.72 (m, 4H); MS *m*/*z* 147 (M^+). Anal. Calcd for $C_{10}H_{13}N$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.50; H, 8.90, N, 9.45.

2-Methyl-5,6,7,8-tetrahydroquinoline (5d): 66 mg (45%), $bp_{20\ mmHg}$ 128−30 °C (lit.[27] $bp_{12\ mmHg}$ 101−104 °C), R_f = 0.75 (toluene); IR ν_{max} (KBr) 2910, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (d, 1H, *J* = 9 Hz), 7.30 (d, 1H, *J* = 9.0 Hz), 2.80−2.65 (m, 4H), 2.13 (s, 3H), 1.90−1.65 (m, 4H); MS *m*/*z* 147 (M^+).

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Supporting Information Available: The IR, ^1H and ^{13}C NMR, and mass spectral data for compounds **3b**−**h**. The material is available free of charge via the Internet at http://pubs.acs.org.

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