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Note

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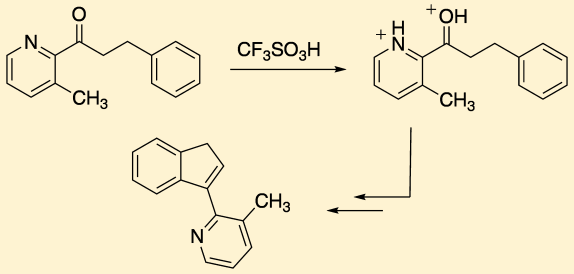
Cyclodehydrations Leading to Indene Products Having N-Heterocyclic Substituents

Kenneth N. Boblak and Douglas A. Klumpp*

Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, Illinois 60115, United States

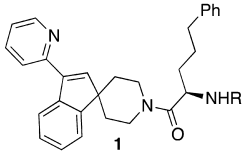
Supporting Information

ABSTRACT: In this Note, we describe superacid-promoted cyclodehydrations leading to functionalized indenes. The product indenes are synthesized having N-heterocyclic substituents, including pyridyl, imidazolyl, pyrimdyl, and other groups. A mechanism is proposed involving dicationic, superelectrophilic intermediates. The protonated N-heterocyclic rings are shown to dramatically lower the LUMO energy level of the carboxonium electrophile (compared to that of a similar uncharged system).



Functionalized indenes are useful scaffolds in synthetic and medicinal chemistry.[1] For example, indenes with N-heterocyclic substituents have been utilized as pharmaceutical agents and metal ligands. 2-(1*H*-Inden-3-yl)pyridine compounds (**1**) were examined by Merck researchers for use as growth hormone release promoters,[2] whereas compound **2** (*fenistil*) is a well-known antihistamine drug.[3] Pyridyl-substituted indenes have also been used to prepare zirconium (**3**),[4] manganese (**4**),[5] and ruthenium complexes.[6]

Cyclodehydration is a well-known route to carbocyclic products.[7] For example, many polycyclic aromatic hydrocarbons have been prepared using this chemistry.[8] Product ring systems include dihydronaphthalenes and indenes. The conversions involve the acid-promoted reactions of aldehydes, ketones, or analogous substrates, and they often occur through carboxonium ion intermediates. Over the years, we have described several types of superelectrophilic condensation reactions involving dicationic carboxonium ions.[9,10] These types of reactive intermediates have shown high reactivities in Friedel–Crafts-type reactions. In this Note, we describe a cyclodehydration to give indenes with heterocyclic substituents, and a mechanism is proposed involving dicationic carboxonium ions as the key intermediates.



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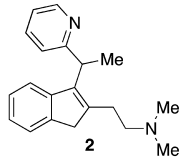

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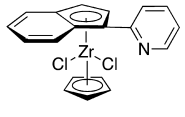

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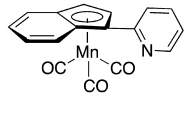

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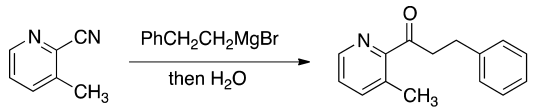
To begin our studies, we sought to prepare dihydrocinnamoyl-substituted heterocycles. Two approaches were found to be useful, one involving the reaction of a heterocyclic nitrile with phenethylmagnesium bromide (eq 1) and another



(1)

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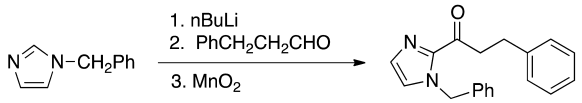
involving formation of the heterocyclic organolithium reagent (eq 2).A series of dihydrocinnamoyl-substituted heterocycles



(2)

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was prepared and combined with superacidic, CF_3SO_3H, to give the cyclodehydration products (Table 1). In general, the expected indene products were formed in good yields. The indenes were found to be somewhat unstable unless they were stored at a low temperature under an inert atmosphere. The product indenes include pyridyl, pyrimidyl, imidazolyl, oxazolyl, thiazolyl, and benzothiazolyl derivatives (**14**–**20**). Cyclization of ketone **13** leads to the analogue of *fenistil*, a functionalized indene (**21**), rather than a product having an exocyclic double bond. Good conversion of **7** to **14** was also accomplished using perfluoro(2-ethoxyethane)sulfonic acid, another Brønsted superacid. Other acids, such as concentrated sulfuric acid, trifluoroacetic acid, $BF_3{\cdot}OEt_2$, and $TiCl_4$, did not promote the conversion to **14** in reactions at 25 °C. As few as 4 equivalents of CF_3SO_3H promotes the cyclization of **7** to **14**, but the

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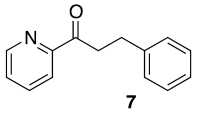
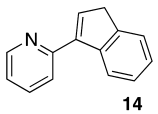
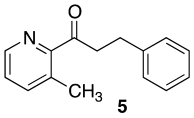
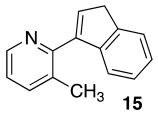
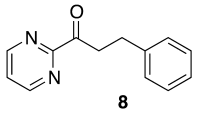
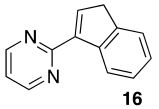
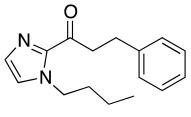
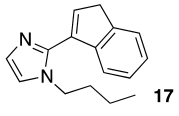
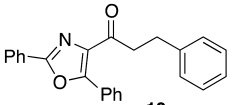
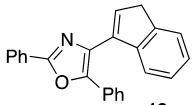
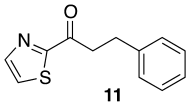
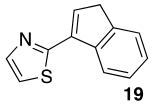
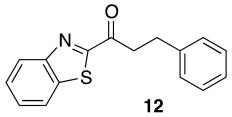
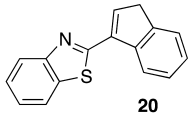
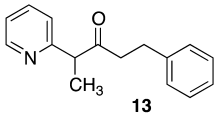
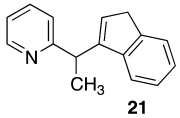
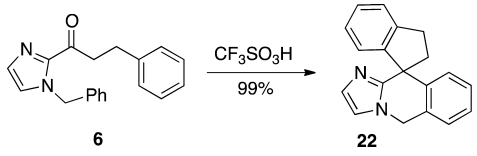
Table 1. Products and Yields from the Cyclodehydration Reactions of Ketones 5 and 7−13 with CF_3SO_3H

Substrate	Product	Yield[a]
 7	 14	76%
 5	 15	87%
 8	 16	69%
 9	 17	98%
 10	 18	70%
 11	 19	80%
 12	 20	80%
 13	 21	75%

[a]Isolated yield of purified product.

synthesis proceeds to 100% conversion within 4 h when 12 or more equivalents of acid are used. The CF_3SO_3H may be quantitatively recycled using a published procedure (see Experimental).

When the ketone substrates have pendant aryl groups, they have the capability of undergoing a second cyclization, leading to spirocyclic indanes (eqs 3 and 4).Thus, the imidazole and quinolone derivatives (**6** and **23**) provide the respective spirocyclic products (**22** and **24**) in excellent yields.



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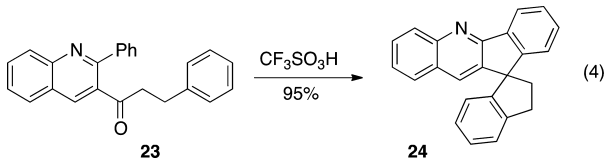
In these dehydrative cyclizations, a mechanism is proposed involving a series of dicationic intermediates (Scheme 1). Protonation of the pyridyl nitrogen and the carbonyl group leads to superelectrophilic carboxonium ion intermediate **25**.



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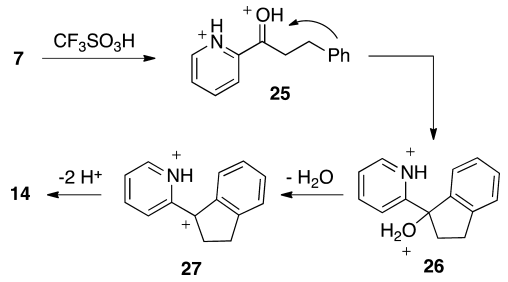
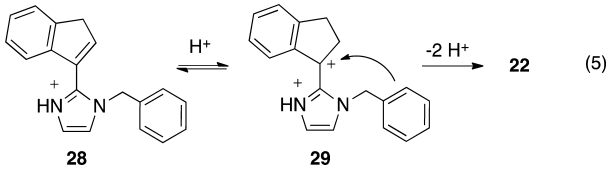
Scheme 1

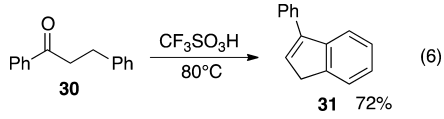


Cyclization of carboxonium ion **25** provides dicationic oxonium ion **26**, and dehydration gives carbocation **27**. Deprotonation steps then give the observed indene product, **14**. In the case of spirocyclic product **22**, the indenyl intermediate (**28**) is likely in equilibrium with the superelectrophilic carbocation (**29**), as small amounts of the corresponding indene product may be isolated if the reaction is done at low temperature (eq 5). Thus, superelectrophile **29** undergoes cyclization with the benzyl group to give product **22**. A similar process is envisaged for spirocyclic product **24**.



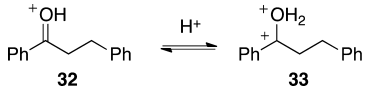
(5)

In order to evaluate the effects of the pyridinium ring on the cyclodehydration, the cyclization of compound **7** was compared with the same reaction involving 1,3-diphenylpropan-1-one (**30**).[11] Previous work by Shudo and Ohwada estimated the pK_{BH^+} value for compound **30** to be −5.9 in CF_3SO_3H–CF_3CH_2OH solution.[11] Cyclodehydration of **30** may be accomplished in good yield with CF_3SO_3H (H_o −14), but it requires elevated temperature (eq 6). NMR experiments



(6)

indicated that compound **30** is completely protonated in solutions more acidic than H_o −9, and evidence from kinetic experiments have suggested the involvement of superelectrophile **33** as the key reactive intermediate in the cyclodehydration (eq 7). If the monocationic species (**32**) undergoes cyclization to the indene, it does so at an exceedingly slow rate.[11]



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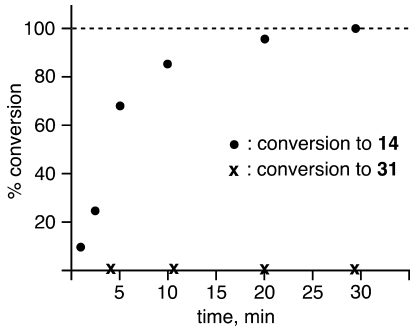

Figure 1. Cyclodehydrations (7 → **14** and **30** → **31**) in excess CF_3SO_3H (22 equiv) at 25 °C.

Both compounds **7** and **30** were mixed with excess CF_3SO_3H, and the relative rates of cyclization were compared (Figure 1). The conversions were done by combining a solution of the ketone in CH_2Cl_2 with CF_3SO_3H, and the mixture was quenched after the reaction period. The product mixtures were then subjected to GC-FID analysis. Heterocyclic ketone **7** was completely converted to the indene condensation product (**14**) within 30 min. Conversely, no detectable condensation product **31** was observed during the same reaction period from 1,3-diphenylpropan-1-one (**30**). This is consistent with Shudo and Ohwada's observation that forcing conditions are required for cyclodehydration of compound **30** in CF_3SO_3H.

At 25 °C, the reaction of **30** with CF_3SO_3H presumably involves formation of the monocation carboxonium ion intermediate (**32**) with little or no superelectrophile (**33**) formation. Thus, indene **31** is not produced.

The facile cyclodehydration of compound **7** may be understood with the involvement of dicationic intermediate **25**. Previous work has shown the activating effects of protonated N-heterocyclic rings on adjacent electrophilic sites.[12] In this case, the pyridinium ring of **25** enhances the reactivity of the neighboring carboxonium ion group. Several protonated heterocyclic ketones were studied computationally and compared with monocationic intermediates **32** and **34** (Figure 2). Calculations were done at the B3LYP 6-311G(d,p) level, using the Gaussian09 program suite.[13] In all cases, the

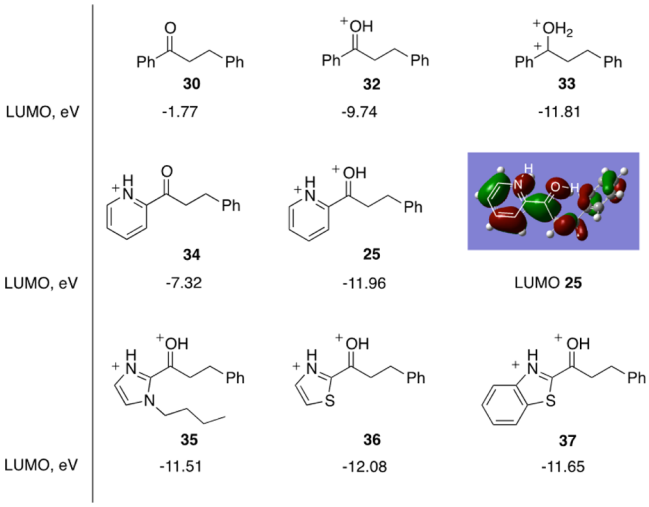

Figure 2. Calculated LUMO energies and the graphical representation of LUMO (**25**).

dicationic species exhibit significantly lowered LUMO orbitals compared to the monocationic species, and, not surprisingly, the LUMO coefficients are high at the carboxonium carbon (see LUMO **25**). Moreover, the heterocyclic dications (**25** and **35**–**37**) all exhibit LUMO energy levels (−11.51 to −12.08 eV) comparable to that of superelectrophilic carboxonium dication **33** (−11.81 eV). Olah and Koltunov have previously correlated the relative reactivities of superelectrophiles with LUMO characteristics.[14] These observations are consistent with the electrophilic activating effects of protonated N-heterocyclic rings. It also is notable that the heterocyclic dications (**25** and **35**–**37**) are formed by protonation of a strong base site, the heterocyclic ring, and a relatively weak base site, the carbonyl group. With superelectrophilic carboxonium dication **33**, superelectrophile formation requires protonation of two weak base sites, the carbonyl group and carboxonium oxygen.

In summary, we have described a convenient route to N-heterocyclic substituted indenes. The chemistry involves a cyclodehydration of 3-phenyl-1-propanones in superacidic solution. The results suggest a significant role of the protonated N-heterocycle in activation of the electrophilic carboxonium ion. Previously, aryl-substituted indenes have been synthesized from the dehydration of functionalized indanols (which were prepared from the corresponding 1-indanones and an organometallic reagent).[15] The present work involving superelectrophilic cyclizations is general in scope, and it improves synthetic access to functionalized indenes, a structure with general utility.

EXPERIMENTAL SECTION

General. All reactions were performed using oven-dried glassware under an argon atmosphere. Trifluoromethanesulfonic acid was freshly distilled prior to use. All commercially available compounds and solvents were used as received. ^1H and ^{13}C NMR were done using a either a 500 or 300 MHz spectrometer; chemical shifts were made in reference to NMR solvent signals. Low-resolution mass spectra were obtained from a gas chromatography instrument equipped with a mass-selective detector, whereas high-resolution mass spectra were obtained from a commercial analytical laboratory (electron impact ionization; sector instrument analyzer type). Triflic acid may also be recovered and recycled quantitatively.[16]

Preparation of 1,3-Diarylpropan-1-one Derivatives, General Method A. The heterocyclic nitrile (2 mmol) is dissolved in anhydrous ether (20 mL) and cooled to 0 °C. To this solution is slowly added phenethylmagnesium chloride (2.4 mL, 1.0 M in THF), and the mixture is stirred for 2 h at 0 °C, warmed to 25 °C, and quenched with ca. 3 mL of 1.0 M HCl. This solution is stirred overnight. Following neutralization with 2 M NaOH, the product mixture is partitioned between ether and water. The aqueous phase is subjected to two further extractions with ether, and the combined ether extracts are washed with water and then brine. After drying the solution with anhydrous Na_2SO_4, the solvent is evaporated. The product, 1,3-diarylpropan-1-one, may be purified by column chromatography (silica gel, ether/hexane or ethyl acetate/hexane).

Preparation of 1,3-Diarylpropan-1-one Derivatives, General Method B. The heterocyclic substrate (2 mmol) is dissolved in anhydrous THF (15 mL), the solution is cooled to −78 °C, and an *n*-BuLi solution (5.25 mL, 2.5 M in THF, 2.1 mmol) is added slowly with stirring. Following a 2 h period, hydrocinnamaldehyde (2 mmol in 5 mL of THF) is added, and the solution is allowed to warm to room temperature. Stirring for 2 h is followed by a workup procedure: water (20 mL) is added to the mixture, the organic phase is partitioned off, and the aqueous phase is extracted twice ether. The combined organic extracts are washed twice with brine and then dried with anhydrous sodium sulfate. The crude alcohol is then isolated by removal of solvent with reduced pressure. The crude alcohol is

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oxidized to the corresponding ketone using an adapted procedure from the literature.[17]

Cyclodehydration to the Heterocyclic Indenes, General Method C. The heterocyclic ketone (1 mmol) is dissolved in CH_2Cl_2 (2 mL), and CF_3SO_3H (1 mL, 11 mmol) is added to the stirred solution. After 4 h, the mixture is poured over ca. 10 g of ice and 50 mL $CHCl_3$. The aqueous layer is then made basic (ca. pH 8) by addition of 10 M NaOH, and the mixture is partitioned in a separatory funnel. The aqueous layer is extract twice with $CHCl_3$, the combined organic extracts are washed with water and then brine, and the solution is dried over anhydrous sodium sulfate. Although the indene products are often obtained in greater than 95% purity, the products may be further purified with silica gel chromatography.

1-(3-Methylpyridin-2-yl)-3-phenylpropan-2-one (5). Using general method A, 3 methyl-2-pyridinecarbonitrile (0.236 g, 2.0 mmol) gives compound **5** (0.391g, 1.74 mmol, 87%), isolated as a clear, yellow oil, R_f = 0.30 (4:1 hexane:ether). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, 3H), 3.07 (t, J = 7.4 Hz, 2H), 3.58 (t, J = 8.0 Hz, 2H), 7.17−7.35 (m, 6H), 7.55 (dq, J = 0.7, 1.6, 7.7 Hz, 1H), 8.50 (dd, J = 1.2, 4.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.2, 30.1, 41.4, 125.9, 126.0, 128.4, 128.5, 134.4, 140.1, 141.5, 146.1, 151.8, 203.2. LR-MS (EI): 225 (M+), 197, 182, 93, 65. HR-MS (EI) calcd for $C_{15}H_{15}NO$, 225.1154; found, 225.1157.

1-(1-Benzyl-1*H*-imidazol-2-yl)-3-phenylpropane-1-one (6). Using general method B, 1-benzylimidazole (0.63 g, 4.0 mmol) gives compound **6** (0.79 g, 2.7 mmol, 68%), isolated as clear, yellow oil, R_f = 0.12 (5:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.07 (t, J = 7.7 Hz, 2H), 3.54 (t, J = 8.0 Hz, 2H), 5.65 (s, 2H), 7.10 (d, J = 0.8 Hz, 1H), 7.19−7.23 (m, 4 H), 7.28−7.39 (m, 7H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.0, 40.7, 51.8, 126.1, 127.6, 128.1, 128.4, 128.5, 128.9, 129.5, 136.4, 141.0, 142.4, 192.1. LR-MS (EI): 290 (M+), 262, 185, 157, 91. HR-MS (EI) calcd for $C_{19}H_{18}N_2O$, 290.1419; found, 290.1419.

3-Phenyl-1-(pyridin-2-yl)propan-1-one (7).[17] Using general method A, 2-cyanopyridine (0.507 g, 4.9 mmol) gives compound **7** (0.90 g, 4.3 mmol, 88%), isolated as a clear, light yellow oil, R_f = 0.27 (4:1 hexane/ether). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.09 (t, J = 7.9 Hz, 2H), 3.60 (t, J = 7.95 Hz, 2H), 7.17−7.24 (m, 1H), 7.27−7.34 (m, 4H), 7.48 (dq, J = 7.6, 4.8, 1.2 Hz, 1H), 7.84 (dt, J = 7.7, 1.7 Hz, 1H), 8.1 (dt, J = 7.9, 1.1 Hz, 1H), 8.68 (dq, J = 4.7, 1.7. 0.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.9, 39.4, 121.8, 126.0, 127.1, 128.4, 128.5, 136.9, 141.4, 148.9, 153.3, 201.0. LR-MS (EI): 211 (M+), 183, 182, 107, 91, 79. HR-MS (EI) calcd for $C_{14}H_{13}NO$, 211.0997; found, 211.0996.

3-Phenyl-1-(pyrimidin-2-yl)propan-1-one (8). Using general method A, 2-cyanopyrimidine (0.5035 g, 4.8 mmol) gives compound **8** (0.808 g, 3.8 mmol, 80%), isolated as clear, yellow oil, R_f = 0.6 (100% ether). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.13 (t, J = 7.2 Hz, 2H), 3.60 (t, J = 8.1 Hz, 2H), 7.13−7.31 (m, 6H), 7.46 (t, J = 4.8 Hz, 1H), 8.93 (d, J = 4.9, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.8, 40.8, 124.0, 136.1, 128.5, 128.5, 141.1, 157.6, 160.0, 198.9. LR-MS (EI): 212 (M+), 183, 169, 105, 80. HR-MS (EI) calcd for $C_{13}H_{12}N_2O$, 212.0950; found, 212.0952.

1-(1-Butyl-1*H*-imidazol-2-yl)-3-phenylpropan-1-one (9). Using general method B, 1-butylimidazole (0.5 mL, 3.83 mmol) gives compound **9** (0.673 g, 2.63 mmol, 69%), isolated as a clear, light brown oil, R_f = 0.11 (5:1 hexane/ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.26−1.34 (m, 2H), 1.67−1.73 (m, 2H), 3.04 (t, J = 7.5 Hz, 2H), 3.48 (t, J = 8.0 Hz, 2H), 4.34 (t, J = 7.4 Hz, 2H), 7.01 (d, J = 0.8 Hz, 1H), 7.10 (d, J = 0.9 Hz, 1H), 7.12−7.17 (m, 1H), 7.24 (s, 2H), 7.25 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6, 19.7, 30.0, 33.1, 40.7, 48.4, 125.9, 125.9, 128.3, 128.4, 129.0, 141.1, 142.3, 191.7. LR-MS (EI): 256 (M+), 228, 199, 123, 82. HR-MS (EI) calcd for $C_{16}H_{20}N_2O$, 256.1576; found, 256.1569.

1-(2,5-Diphenyloxazol-4-yl)-3-phenylpropan-1-one (10). Using general method B, 2,4-diphenyloxazole (0.442 g, 2.0 mmol) gives compound **10** (0.218 g, 0.62 mmol, 31%), isolated as colorless solid resin (mp 107−109 °C), R_f = 0.18 (5:1 hexane/ether). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.13 (t, J = 7.4 Hz, 2 H), 3.55 (t, J = 8.2 Hz, 2H), 7.22−7.29 (m, 1H), 7.34 (s, 2H), 7.36 (s, 2H), 7.50−7.57 (m, 6H), 8.13−8.19 (m, 2H), 8.29−8.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.0, 42.7, 126.0, 126.7, 127.3, 128.1, 128.5, 128.5, 128.6, 128.9, 130.6, 131.0, 135.1, 141.5, 153.2, 158.7, 195.9. LR-MS (EI): 353 (M+), 325, 251, 221, 105. HR-MS (EI) calcd for $C_{24}H_{19}NO_2$, 353.1415; found, 353.1414.

3-Phenyl-1-(thiazol-2-yl)propan-1-one (11). Using general method B, thiazole (0.170 g, 2.0 mmol) gives compound **11** (0.207 g, 0.95 mmol, 48%), isolated as clear, colorless oil, R_f = 0.44 (5:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.13 (t, J = 7.6 Hz, 2H), 3.54 (t, J = 7.9 Hz, 2H), 7.21−7.24 (m, 1H), 7.29−7.34 (m, 4H), 7.66 (d, J = 3.1 Hz, 1H), 8.01 (d, J = 3.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.0, 40.1, 126.2, 126.3, 128.49, 128.52, 140.8, 144.8, 167.0, 193.0. LR-MS (EI): 217 (M+), 189, 188, 112, 85. HR-MS (EI) calcd for $C_{12}H_{11}NOS$, 217.0561; found, 217.0562.

1-(Benzo[*d*]thiazol-2-yl)-3-phenylpropan-1-one (12). Using general method B, benzothiazole (0.270 g, 2.0 mmol) gives compound **12** (0.313 g, 1.12 mmol, 59%), isolated as a light yellow solid (mp 69−70 °C) in 59% yield, R_f = 0.47 (5:1 hexane/ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.17, (t, J = 7.5 Hz, 2H), 3.67 (t, J = 8.0 Hz, 2H), 7.23−7.26 (m, 1H), 7.33−7.35 (m, 4H), 7.54−7.62 (m, 2 H), 8.00−8.01 (m, 1H), 8.19−8.21 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.7, 40.4, 122.5, 125.4, 126.3, 127.0, 127.8, 128.6, 137.2, 140.7, 153.5, 166.2, 194.5. LR-MS (EI): 267 (M+), 238, 162, 135, 91. HR-MS (EI) calcd for $C_{16}H_{13}NOS$, 267.0718; found, 267.0717.

1-Phenyl-4-(pyridin-2-yl)pentan-3-one (13). 2-Ethylpyridine (0.286 mL, 2.5 mmol) is dissolved in 15 mL of THF, and the solution is cooled to −5 °C. *n*-BuLi (1.0 mL, 2.5 M solution in hexanes, 2.5 mmol) was added, and this solution is stirred for 45 min. To this solution is added 0.328 mL of hydrocinnamonitrile (0.328 g, 2.5 mmol), and the mixture is allowed to stir for 30 min. Following this period, 2 M HCl (30 mL) is added, and the solution is stirred for 10 min. The solution is made basic with a 10% NaOH solution and extracted three times with $CHCl_3$. The organic extracts are combined, washed with H_2O and then brine, and dried over sodium sulfate, and the solvent is evaporated. Compound **13** is isolated as a clear, yellow oil (0.1089 g, 0.46 mmol, 18%), R_f = 0.20 (4:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (d, J = 7.0 Hz, 3H), 2.72−2.80 (m, 2H), 2.84−2.92 (m, 2H), 4.00 (q, J = 7.0, 1H), 7.08−7.25 (m, 7H), 7.60−7.65 (td, J = 7.7 Hz, 1.9 Hz, 1H), 8.54−8.56 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.2, 29.8, 42.9, 55.3, 122.1, 122.3, 126.0 128.3, 128.4, 137.0, 141.0, 139.5 160.0. LR-MS (EI): 239 (M+), 224, 107, 106, 91. HR-MS (EI) calcd for $C_{16}H_{17}NO$, 239.1310; found, 239.1311.

2-(1*H*-Inden-3-yl)pyridine (14).[18] Using general method C, ketone **7** (0.216 g, 1.02 mmol) gives compound **14** (0.149 g, 0.774 mmol, 76%) as a yellow resin, R_f = 0.26 (9:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.58 (d, J = 2.2 Hz, 2H), 7.01 (t, J = 2.2 Hz, 1H), 7.24−7.33 (m, 2H), 7.40 (t, J = 7.9, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.69−7.79 (m, 2H), 8.15 (d, J = 7.6 Hz, 1H), 8.75−8.77 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.3, 122.0, 122.03, 122.2, 123.9, 125.1, 126.3, 133.9, 136.4, 142.9, 144.1, 144.6, 149.4, 154.9. LR-MS (EI): 211 (M+), 183, 182, 107, 91, 79. HR-MS (EI) calcd for $C_{14}H_{13}NO$, 211.0997; found, 211.0996.

2-(1*H*-Inden-3-yl)-3-methylpyridine (15). Using general method C, ketone **5** (0.2251 g, 1.0 mmol) provides compound **15** (0.1749 g, 0.85 mmol, 87%) as a clear, orange oil, R_f = 0.21 (7:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.37 (s, 3H), 3.61 (d, J = 1.8 Hz, 2H) 6.68 (t, J = 1.8 Hz, 1H), 7.20−7.39 (m, 4H), 7.54−7.57 (m, 1H), 7.61−7.66 (m, 1H), 8.59 (d, J = 3.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.6, 38.6, 121.1, 122.2, 123.8, 124.9, 126.2, 132.0, 133.4, 138.2, 143.8, 143.8, 144.3, 146.9, 154.4. LR-MS (EI): 207 (M+), 206, 180, 102. HR-MS (EI) calcd for $C_{15}H_{13}N$, 207.10480; found, 207.10441.

2-(1*H*-Indene-3-yl)pyrimidine (16). Using general method C, ketone **8** (0.1051 g, 0.496 mmol) provides compound **16** (0.0662 g, 0.341 mmol, 69%) as a clear, dark red resin, R_f = 0.21 (9:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.63 (d, J = 2.1 Hz, 2H), 7.19−7.22 (m,1H), 7.28−7.34 (m, 2H), 7.40−7.57 (m, 2H), 7.68 (t, J = 2.1 Hz, 1H) 8.57 (d, J = 7.7 Hz, 1H), 8.85 (d, J = 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.3, 119.0, 123.3, 123.8, 125.1, 123.4,

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128.5, 139.4, 142.9, 144.9, 156.9, 163.1. LR-MS (EI): 194 (M+), 193, 168, 140, 115. HR-MS (EI) calcd for $C_{13}H_{10}N_2$, 194.08440; found, 194.08441.

1-Butyl-2-(1*H*-inden-3-yl)-1*H*-imidazole (17). Using general method C, ketone **9** (0.121g, 0.472 mmol) provides compound **17** (0.110 g, 0.462 mmol, 98%) as a brown oil, R_f = 0.22 (1:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.78 (t, J = 7.5 Hz, 3H), 1.13−1.23 (m, 2H) 1.69−1.75 (m, 2H), 3.66 (s, 2H), 4.12 (t, J = 7.5 Hz, 2H), 7.19 (s, 1H). 7.22−7.32 (m, 3H), 7.40 (s, 1H), 7.52−7.53 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.3, 19.3, 32.3, 39.8, 48.4, 120.1, 120.7, 121.9, 124.6, 126.7, 127.0, 127.3, 140.0, 140.3, 143.1, 143.4. LR-MS (EI): 238 (M+), 223, 209, 182, 127. HR-MS (EI) calcd for $C_{16}H_{18}N_2$, 238.14700; found, 238.14720.

4-(1*H*-Inden-3-yl)-2,5-diphenyloxazole (18). Using general method C, ketone **10** (0.1195 g, 0.339 mmol) provides compound **18** (0.0798 g, 0.238 mmol, 70%) as a clear, light brown oil, R_f = 0.65 (9:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.63 (d, J = 2.1 Hz, 2H), 6.93 (t, J = 1.8 Hz, 1H), 7.25−7.57 (m, 10H), 7.71−7.74 (m, 2H), 8.20−8.23 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.77, 121.62, 123.76, 125.08, 126.19, 126.50, 127.38, 128.29, 128.58, 128.71, 128.79, 130.40, 131.90, 134.34, 136.52, 143.18, 143.98, 146.81, 160.13. LR-MS (EI): 335 (M+), 306, 231, 2−3, 202, 77. HR-MS (EI) calcd for $C_{24}H_{17}NO$, 335.13102; found, 335.13051.

2-(1*H*-Inden-3-yl)thiazole (19). Using general method C, ketone **11** (0.1088 g, 0.5 mmol) provides compound **19** (0.0856 g, 0.043 mmol, 86%) as a white solid (mp 96−102 °C), R_f = 0.40 (9:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.61 (d, J = 2.3, 2H), 7.17 (t, J = 2.3 Hz, 1H), 7.28−7.36 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.96 (d, J = 3.3 Hz, 1H), 8.33 (d, J = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.5, 118.2, 122.2, 123.9, 125.7, 126.6, 135.1, 138.0, 141.6, 143.2, 144.0, 163.3. LR-MS (EI): 199 (M+), 154, 140, 115, 58. HR-MS (EI) calcd for $C_{12}H_9NS$, 199.04557; found, 199.04520.

2-(1*H*-Inden-3-yl)benzo[*d*]thiazole (20). Using general method C, ketone **12** (0.1321 g, 0.514 mmol) provides compound **20** (0.0982 g, 0.394 mmol, 77%) as a light gray solid (mp 100−102 °C), R_f = 0.34 (9:1, hexane/ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.66 (d, J = 2.2 Hz, 2H), 7.30 (t, J = 2.3 Hz, 1H), 7.37 (td, J = 1.1, 7.5 Hz, 1H), 7.4 (td, J = 1.1, 7.5 Hz, 1H), 7.49 (t, J = 7.3 Hz, 1H), 7.53−7.58 (m, 2H), 7.94 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 8.57 (d, J = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.8, 121.4, 122.8, 123.6, 123.9, 125.4, 125.9, 126.2, 126.7, 134.4, 137.9, 138.6, 141.5, 143.9, 154.0, 163.0. LR-MS (EI): 249 (M+), 217, 140, 115. HR-MS (EI) calcd for $C_{16}H_{11}NS$, 249.06122; found, 249.06088.

2-(1-(1*H*-Inden-3-yl)ethyl)pyridine (21). Using general method C, ketone **13** (0.1070 g, 0.45 mmol) provides compound **21** (0.0917 g, 0.415 mmol, 92%) as a yellow oil, R_f = 0.24 (9:1, hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.73 (d, J = 7.2 Hz, 3H), 3.44 (s, 2H), 4.33 (dt, J = 7.1 Hz, 1.7 Hz, 1H), 6.46 (d, J = 1.7 Hz, 1H), 7.11 (ddd, J = 7.45 Hz, 4.90 Hz, 1.10 Hz, 1H), 7.16−720 (m, 4H), 7.45−7.49 (m, 1H), 7.55 (td, J = 15.37 Hz, 1H), 8.60−8.63 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.1, 37.8, 41.6, 120.1, 121.4, 121.7, 123.7, 124.6, 125.9, 128.6, 136.6, 144.6, 144.7, 147.2, 149.2, 164.4). LR-MS (EI): 221 (M+), 220, 206, 204, 115. HR-MS (ESI) calcd for $C_{16}H_{16}N$, 222.1283; found, 222.1286.

2′,3′-Dihydro-5*H*-spiro[imidazo[1,2-*b*]isoquinoline-10,1′-indene] (22). Using general method C, ketone **6** (0.1256 g, 0.433 mmol) provides compound **22** (0.1171 g, 0.431 mmol, 98%) as a transparent, yellow oil, R_f = 0.27 (1:1, hexane/ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.54−2.59 (m, 1H), 2.76−2.81 (m, 1H), 3.19−3.25 (m, 1H), 3.43−3.49 (m, 1H), 5.52 (d, J = 17.0 Hz, 1H), 5.67 (d, J = 17 Hz, 1H), 6.82, (d, J = 7.7 Hz, 1H), 6.82 (dd, J = 0.8, 7.7 Hz, 1H), 7.18−7.21 (m, 1H), 7.28−7.44 (m, 6H), 7.62 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.8, 43.0, 48.2, 52.4, 120.2, 120.7, 142.7, 125.9, 126.3, 126.9, 127.1, 128.1, 128.2, 129.3, 129.5, 136.8, 142.4, 144.4, 148.4. LR-MS (EI): 272 (M+), 271, 257, 230, 202, 128. HR-MS (EI) calcd for $C_{19}H_{16}N_2$, 272.13135; found, 272.13185.

3-Phenyl-1-(2-phenylquinolin-3-yl)propan-1-one (23). 2-Phenylquinoline-3-carbaldehyde (0.117 g, 0.50 mmol) is dissolved in 15 mL of anhydrous ether, and the solution is cooled to 0 °C. To this solutionis added phenethylmagnesium chloride (0.6 mL, 1.0 M in THF, 0.6 mmol), and the mixture is stirred at room temperature for 4 h. The reaction mixture is then quenched with slightly acidic water (20 mL of H_2O with several drops of 1.0 M HCl), and 40 mL of ether is added. The products are extracted into the ether. The resulting organic solution is washed with brine and dried with anhydrous sodium sulfate. The crude alcohol is oxidation to provide the crude ketone.[19] Ketone **23** is isolated (0.114 g, 0.34 mmol, 68%) as a colorless oil, R_f = 0.51 (5:1 hexane/ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.73 (t, J = 7.3 Hz, 2H), 2.85 (t, J = 7.8 Hz, 2H), 6.96 (d, J = 7.1 Hz, 2H), 7.14−7.29 (m, 3H), 7.53, (d, J = 1.4 Hz, 1H), 7.54 (d, J = 1.8 Hz, 2H), 7.63−7.66 (m, 1H), 7.69−7.71 (m, 2H), 7.85−7.88 (m, 1H), 7.93 (d, J = 7.7 Hz, 1H), 8.30 (s, 1H), 8.34 (d, J = 7.9, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.7, 44.6, 126.1, 126.2, 127.6, 128.3, 128.4, 128.42, 128.96, 129.0, 129.3, 129.7, 131.7, 134.8, 137.4, 140.3, 147.5, 156.3, 204.8. LR-MS (EI): 337 (M+), 246, 232, 204, 176. HR-MS (EI) calcd for $C_{24}H_{19}NO$, 337.1466; found, 337.1467.

2,3-Dihydrospiro[indene-1,11′-indeno[1,2-*b*]quinoline (24). Using general method C, ketone **23** (0.0233 g, 0.069 mmol) provides compound **24** (0.0209 g, 0.066 mmol, 95%) as an oil, R_f = 0.38 (4:1, hexane/ether). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.66−2.77 (m, 2H), 3.42−3.51 (m, 2H), 6.53 (d, J = 7.6 Hz, 1H) 7.02−7.06 (m, 1H), 7.25−7.33 (m, 2H), 7.43−7.55 (m, 4H), 7.68−7.74 (m, 2H), 7.89 (s, 1H), 8.27 (dd, J = 8.3, 25.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.0, 40.7, 60.7, 121.8, 123.7, 124.1, 125.0, 125.8, 127.2, 127.5, 127.9, 128.0, 128.1, 129.0, 129.1, 130.1, 131.0, 138.7, 144.2, 144.6 147.5, 148.5, 154.2, 160.5. LR-MS (EI): 319 (M+), 318, 304, 152. HR-MS (EI) calcd for $C_{24}H_{17}N$, 319.13610; found, 319.13566.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Computational procedures and results, characterization data, and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dklumpp@niu.edu.

Notes

The authors declare no competing financial interest.

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