Unusual 1,4-Addition of 2-Pyridyl Carboxylates to Benzynes: A Convenient Route to 1-(2-Acylphenyl)-2-pyridones

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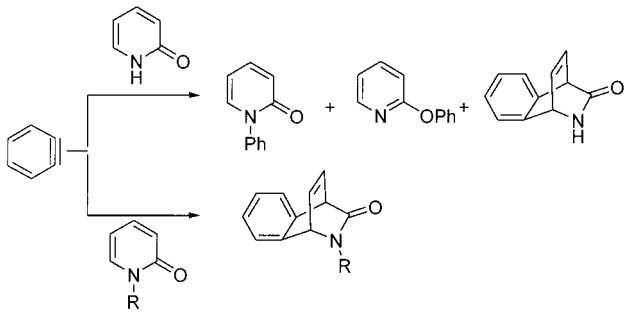
The chemistry of benzyne has been well incorporated into the arsenal of synthetic chemistry, and today it is accepted as a valuable addition to synthetic design.[1] This unstable intermediate exhibits a wide range of reactivity including electrophilic attack,[2] dimerization, and trimerization[3] as well as [2 + 2] and [4 + 2] cycloadditions[4,5] with enes or dienes. One of these reactions receiving considerable attention is the reaction with 2-pyridones that shows interesting regio- and chemoselectivity.[6] When benzyne is treated with 1-substituted-2-pyridones only cycloaddition products[7,8] are observed, whereas unsubstituted 2-pyridones provide both [4 + 2] cycloaddition and Micheal type addition products (Scheme 1).[6,9] In the latter case, both N- and O-arylation take place to yield 1-phenyl-2-pyridone and 2-phenoxypyridine, respectively, because of the tautomeric nature of 2-pyridones. These interesting observations raise the question whether a pure tautomer of 2-pyridones will react with benzyne to give any addition products. 2-Pyridyl carboxylates **2**, which can be prepared in good yield as pure isomers, may be considered as tautomers of the corresponding *N*-acyl 2-pyridones. In this paper, we wish to report for the first time the addition chemistry of 2-pyridyl carboxylates with benzynes. The reaction displays an unprecedented 1,4-addition of 2-pyridyl carboxylate to benzyne at 1,2-positions. This new addition reaction offers a simple and mild method for the introduction of an amide and a carbonyl to an aromatic ring at ortho positions.

Scheme 1



2-Pyridyl acetate (**2a**) was prepared in a pure tautomeric form from 2-pyridone and acetyl chloride in the presence of potassium carbonate in acetone. This product was identified by comparing the spectral data with those reported in the literature.[10] The reaction of 2-pyridyl acetate (**2a**) with benzyne, generated in situ from isoamyl nitrite and anthranilic acid, proceeds smoothly to give 1-(2-acetylphenyl)-2-pyridones (**3a**) in 58% yield. The product is fully characterized by its spectral data. The presence of an α,β-unsaturated lactam group is evidenced by the observation of a υ_{CO} absorption approximately at 1664 cm^{-1} in the IR spectrum and the resonance at around 162 ppm in the ^{13}C NMR spectrum. The coupling pattern and the number of signals in the ^{1}H NMR are in agreement with a 1,2-disubstituted benzene derivative of the product. The present reaction may be viewed as a 1,4-addition of 2-pyridyl acetate to the carbon−carbon triple bond of benzyne leading to a disubstituted benzene derivative. The reaction involves the formation of a new C−N and C−C bonds with the cleavage of a C−O bond. To the best of our knowledge, it is the first time that 1,4-addition of a 2-pyridyl carboxylate to an unsaturated species is reported. In addition, there are very few examples of addition to benzyne that resulted in the formation of disubstituted product.[11]

In view of the novelty and potential of this reaction for the synthesis of aromatic compounds, we decided to investigate this 1,4-addition reaction of 2-pyridyl carboxylates to benzyne further in details. 2-Pyridyl carboxylates were synthesized according to the procedures similar to that for **2a** by treating the corresponding acid

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Scheme 2

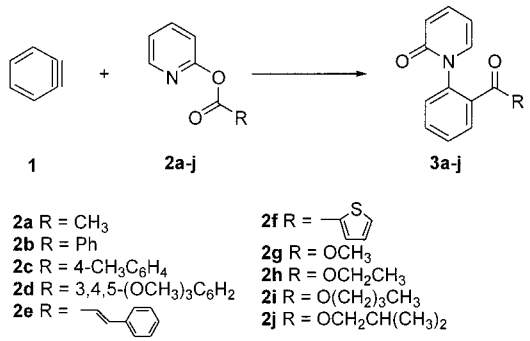
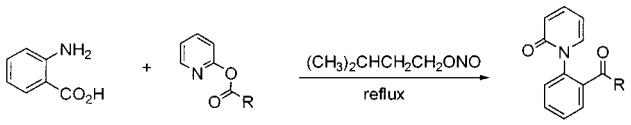
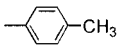
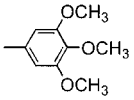
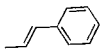


Table 1. Reaction of Benzyne with 2-Pyridyl Carboxylates and 2-Pyridyl Carbonates in Dichloromethane−Acetone Solution



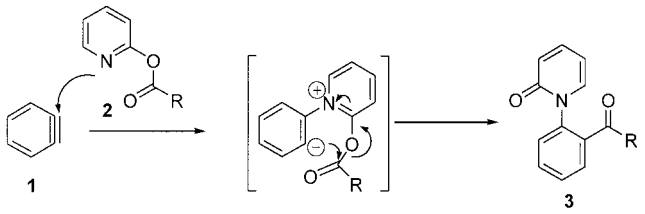
entry	substrate R		product	yield (%)[a]
1	—CH_3	**2a**	**3a**	58
2		**2b**	**3b**	74
3		**2c**	**3c**	70
4		**2d**	**3d**	66
5		**2e**	**3e**	57
6		**2f**	**3f**	48
7	—OCH_3	**2g**	**3g**	64
8	—OCH_2CH_3	**2h**	**3h**	59
9	—$OCH_2CH_2CH_2CH_3$	**2i**	**3i**	49
10	—$OCH_2CHCH_3(CH_3)$	**2j**	**3j**	51

[a] Isolated yields.

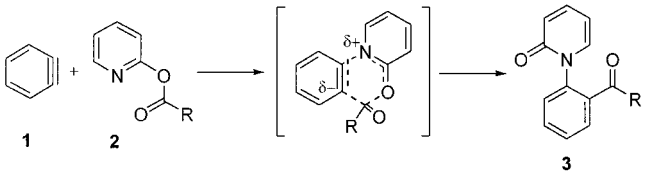
chlorides with 2-pyridones in the presence of potassium carbonate in acetone. The 1,4-addition of **2** to benzyne was carried out in a refluxing dichloromethane solution consisting of **2** and isoamyl nitrite. Anthranilic acid in acetone was added slowly. The procedure was employed for the addition of **2b**−**f** with benzyne. In all cases, the 1,4-addition products **3b**−**f** were isolated (Scheme 2).

The results of these reactions are shown in Table 1. Moderate to good yields (48−74%) were obtained, especially when 2-pyridyl substituted benzoates **2b**−**d** were used. The compounds were isolated, in most cases, as stable solids at room temperature after column chromatography. The yield is sensitive to the addition rate of anthranilic acid. In all cases some starting 2-pyridyl-substituted benzoates were recovered, and a side product acridone was observed. The latter was frequently produced from the reaction of benzyne with anthranilic acid during the generation of benzyne.[12] The reaction of benzyne with 2-pyridyl-substituted benzoates gave better yields than with 2-pyridyl acetate, suggesting that negative inductive effect of the aryl group favors 1,4-addition of 2-pyridyl carboxylate.

Scheme 3



Scheme 4



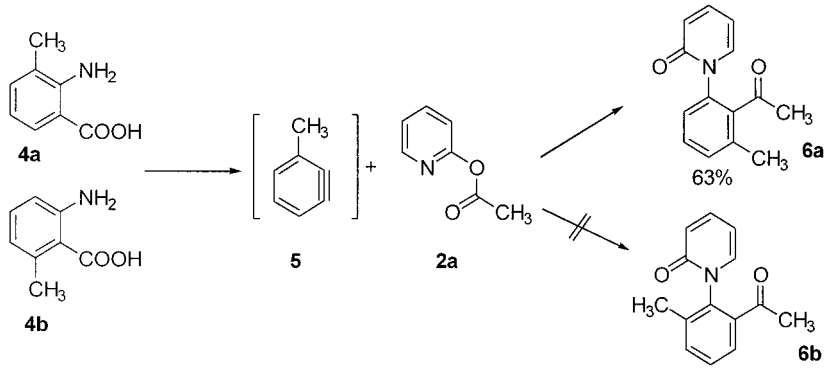
The present methodology was further extended to 2-pyridyl carbonates, prepared by the reaction of alkyl chloroformates with 2-pyridone via an analogous procedure for the synthesis of 2-pyridyl carboxylates **2a**−**f**. Thus, treatment of methyl (2-pyridyl) carbonate (**2g**) with benzyne under similar conditions for 1,4-addition of **2a**−**f** afforded **3g** in 64%. Other 2-pyridyl carbonates **2h**−**j** also reacted successfully with benzyne to give the corresponding addition products **3h**−**j**, respectively, in moderate yields (Table 1, entry 8−10). The structures of all products were also confirmed by their IR, ^{1}H and ^{13}C NMR, and low- and high-resolution mass spectral data. To unambiguously determine the structures of this series of products, the crystal structure of **3g** was determined by X-ray diffraction methods.

The mechanism for this surprising 1,4-addition of 2-pyridyl carboxylate (or carbonate) to benzyne is not entirely clear. Based on the electrophilic nature of the benzyne moiety, we proposed that nucleophilic attack through the nitrogen atom of the pyridyl group at benzyne initiates the addition reaction. Back attack of the resulting carbon anion at the carbonyl carbon of 2-pyridyl carboxylate leads to the cleavage of the ester bond and the formation of the final N-substituted 2-pyridone (Scheme 3). A concerted pathway via a six-membered cyclic transition state with substantial charge redistrubution such as that shown in Scheme 4 leading simultaneously to the C−O bond cleavage and new C−N bond formation also cannot be excluded entirely.

One typical way to prove benzyne as an intermediate reactant is to incorporate substituents to the aromatic ring of anthranilic acid. Thus we have chosen two isomeric anthranilic acids, 3-methylanthranilic acid (**4a**) and 6-methylanthranilic acid (**4b**), for 1,4-addition with compound **2a**. Under the reaction conditions, both substrates should provide the same intermediate **5**, and we should obtain the same product(s) in both cases. Consistent with our anticipation, in both cases only product **6a** was obtained (Scheme 5). The structure of **6a** was determined by spectroscopic measurements and further confirmed by single-crystal X-ray diffraction. This result strongly supports the formation of intermediate benzyne in this reaction. In principle, the reaction of **2a** with the

(12) Sheinin, E. B.; Wright, G. E.; Bell, C. L.; Bauer, L *J. Heterocycl. Chem.* **1968**, *5*, 859 and references therein.

Scheme 5



unsymmetrical benzyne **5** should provide an isomeric mixture **6a** and **6b**. To our surprise, only a single regioisomer **6a** from both reactions was isolated, indicating the addition is completely regioselective. The steric hindrance imparted by the methyl group of phenyl ring likely dictates the observed regioselectivity.

In conclusion, we have observed for the first time the 1,4-addition of 2-pyridyl carboxylate to benzyne to give 1-(2-acylphenyl)-2-pyridones. The methodology offers a simple and mild method for the introduction of an amide and a carbonyl functionality to an aromatic ring at ortho positions. The reactivity of 2-pyridyl carboxylate and carbonate is not completely understood, and further studies are necessary. Extension of this addition chemistry to other electron-withdrawing alkynes and alkenes is possible. Investigation in this direction is underway.

Experimental Section

Procedure for the Synthesis of 2-Pyridyl Carboxylates and Carbonates (2). In a 100-mL round-bottom flask consisting of 2-pyridone (1.90 g, 20 mmol), potassium carbonate (6.91 g, 50 mmol), and acyl chloride (50 mmol) was added dry acetone (40 mL). The mixture was refluxed with stirring for 4 h. The reaction mixture was cooled to room temperature and was filtered through Celite. The filtrate was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed thoroughly with water, and the organic layer was dried over anhydrous $MgSO_4$. After solvent removal, the crude product was obtained in 80−90% yield. Further purification on a silica gel column gave the pure product in about 60−80% yield.

This procedure is similar to those reported previously[10] and the ^{1}H NMR data of **2a** and **2b** are essentially the same as reported. The ^{1}H NMR data of compounds **2c**−**d** and **2g**−**h** are included in Supporting Information.

Synthesis of 1-(2-Acetylphenyl)-1,2-dihydro-2-pyridinone (3a). A solution of anthranilic acid (1.10 g, 0.00802 mol) in acetone (10 mL) was slowly added by syringe pump over 2 h to a refluxing solution of 2-pyridyl acetate (1.0 g, 0.00729 mol) and isoamyl nitrite (1.024 g, 0.00874 mol) in methylene chloride (30 mL). The solution was further refluxed for 5 h. The brown solution was washed with 10% hydrochloric acid (2 × 20 mL) followed by water (2 × 20 mL). The solution was dried over anhydrous $MgSO_4$, and solvent was reduced under reduced pressure. The resulting dark brown oil was subjected to column chromatography over neutral alumina with a mixture of hexane and ethyl acetate (v/v = 3/2) as the eluent to give the desired product in 58% yield. Further recrystallization from dichloromethane and hexane gave **3a** as colorless crystals. Important spectral data follow. Mp = 108 °C; IR (KBr) 3047, 1685, 1664 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50 (3H, s), 6.30 (1H, td, J = 6.6 Hz, J = 1.2 Hz), 6.60 (1H, d, J = 9.6 Hz), 7.27 (1H, dd, J = 6.6 Hz, J = 1.6 Hz), 7.32 (1H, dd, J = 7.2 Hz, J = 2.4 Hz), 7.43 (1H, ddd, J = 9.6 Hz, J = 6.6 Hz, J = 2.0 Hz), 7.52 (1H, td, J = 8.2 Hz, J = 1.6 Hz), 7.62 (1H, td, J = 7.2 Hz, J = 1.2 Hz), 7.73 (1H, dd, J = 8.2 Hz, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 106.1, 121.4, 127.9, 128.2, 128.8, 132.3, 136.9, 137.7, 138.0, 140.3, 162.1, 199.0; HRMS calcd for $C_{13}H_{11}NO_2$ 213.0790, found 213.0791.

Similar procedures were employed for the synthesis of **3b**−**j** and **6a**. Important data of these products are shown below.

1-(2-Benzoylphenyl)-1,2-dihydro-2-pyridinone (3b): mp = 114−115 °C; IR (KBr) 3068, 1659, 1663; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.16 (1H, td, J = 6.6 Hz, J = 1.5 Hz), 6.37 (1H, d, J = 9.2 Hz), 7.23 (1H, td, J = 6.6 Hz, J = 2.1 Hz), 7.27−7.39 (4H, m), 7.48 (3H, td, J = 8.2 Hz, J = 2.0 Hz), 7.60 (1H, td, J = 7.8 Hz, J = 1.6 Hz), 7.80 (2H, dd, J = 8.2 Hz, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 105.7, 121.4, 127.8, 128.1, 129.6, 130.2, 131.6, 133.0, 136.4, 136.8, 138.0, 139.1, 140.0, 161.9, 194.8; HRMS calcd for $C_{18}H_{13}NO_2$ 275.0946, found 275.0944.

1-[2-(4-Methylbenzoyl)phenyl]-1,2-dihydro-2-pyridinone (3c): mp = 146−148 °C; IR (KBr) 3051, 1655, 1649; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (3H, s), 6.16 (1H, td, J = 6.8 Hz, J = 1.4 Hz), 6.39 (1H, d, J = 9.2 Hz), 7.19 (2H, dd, J = 6.8 Hz, J = 1.2 Hz), 7.24 (1H, td, J = 8.8 Hz, J = 1.6 Hz), 7.35 (2H, td, J = 8.2 Hz, J = 2.0 Hz), 7.46−7.47 (2H, m), 7.60 (1H, ddd, J = 8.8 Hz, J = 6.4 Hz, J = 1.6 Hz), 7.70 (2H, dd, J = 8.2 Hz, J = 1.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 105.6, 121.4, 127.9, 128.1, 128.9, 129.4, 130.4, 131.4, 133.8, 137.2, 138.2, 139.0, 140.0, 144.0, 162.0, 194.6; HRMS calcd for $C_{19}H_{15}NO_2$ 289.1103, found 289.1098

1-[2-(3,4,5-Trimethoxybenzoyl)phenyl]-1,2-dihydro-2-pyridinone (3d): mp = 165 °C; IR (KBr) 3038, 1661, 1639; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.80 (6H, s), 3.85 (3H, s), 6.16 (1H, td, J = 6.6 Hz, J = 1.1 Hz), 6.40 (1H, d, J = 9.1 Hz), 7.05 (2H, s), 7.24 (1H, dd, J = 6.6 Hz, J = 2.3 Hz), 7.32 (1H, dd, J = 6.6 Hz, J = 1.5 Hz), 7.38(1H, d. J = 7.6 Hz), 7.50 (2H, dd, J = 9.1 Hz, J = 2.2 Hz), 7.62 (1H, dd, J = 7.6 Hz, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.2, 60.7, 105.8, 107.7, 121.4, 128.1, 128.2, 129.5, 131.4, 131.5, 136.9, 138.2, 138.9, 140.1, 142.7, 152.7, 162.0, 194.0; HRMS calcd for $C_{21}H_{19}NO_5$ 365.1263, found 365.1262.

1-{2-[(E)-3-Phenyl-2-propenoyl]phenyl}-1,2-dihydro-2-pyridinone (3e): mp = 119−120 °C; IR (neat) 3060, 1663, 1645, 1610; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.18 (1H, td, J = 6.8 Hz, J = 1.2 Hz), 6.48 (1H, d, J = 9.2 Hz), 6.93 (1H, d, J = 15.6 Hz), 7.23−7.34 (6H, m), 7.43−7.51 (4H, m), 7.54−7.58 (1H, m), 7.66 (1H, dd, J = 8.0 Hz, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 105.8, 121.4, 124.6, 128.0, 128.4, 128.6, 128.7, 128.9, 130.5, 131.6, 134.2, 137.2, 138.0, 138.5, 140.2, 146.3, 162.0, 192.5; HRMS calcd for $C_{20}H_{15}NO_2$ 301.1103, found 301.1096.

1-[2-(2-Thienylcarbonyl)phenyl]-1,2-dihydro-2-pyridinone (3f): mp = 118−120 °C; IR (KBr) 3074, 1667, 1643; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.22 (1H, td, J = 6.8 Hz, J = 1.2 Hz), 6.43 (1H, d, J = 9.2 Hz), 7.18 (1H, t, J = 7.0 Hz), 7.33−7.41 (3H, m), 7.50−7.65 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 105.7, 121.3, 128.3, 128.1, 128.2, 128.3, 129.1, 131.5, 135.9, 136.6, 138.2, 138.6, 140.1, 143.0, 161.9, 186.6; HRMS calcd for $C_{16}H_{11}NSO_2$ 281.0511, found 281.0502.

Methyl 2-(2-oxo-1,2-dihydro-1-pyridinyl)benzoate (3g): mp = 89 °C; IR (KBr) 3019, 1735, 1658; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 (3H, s), 6.23 (1H, td, J = 6.8 Hz, J = 1.1 Hz), 6.60 (1H, d, J = 9.2 Hz), 7.22 (2H, dd, J = 6.8 Hz, J = 1.1 Hz), 7.27 (1H, dd, J = 7.7 Hz, J = 1.1 Hz), 7.40 (1H, ddd, J = 9.2 Hz, J = 6.5 Hz, J = 2.2 Hz), 7.49 (1H, td, J = 7.6 Hz, J = 1.0 Hz), 7.60

(1H, dd, J = 7.7 Hz, J = 1.3 Hz), 8.05 (1H, dd, J = 7.6 Hz, J = 1.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.1, 105.4, 121.1, 127.9, 128.3, 128.8, 131.1, 133.2, 137.5, 140.0, 140.3, 162.4, 165.0; HRMS calcd for $C_{13}H_{11}NO_3$ 229.0739, found 229.0729.

Ethyl 2-(2-oxo-1,2-dihydro-1-pyridinyl)benzoate (3h): mp = 70−71 °C; IR (KBr) 3046, 1727, 1660; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (3H, t, J = 7.2 Hz), 4.18 (2H, q, J = 7.2 Hz), 6.23 (1H, td, J = 6.8 Hz, J = 1.6 Hz), 6.61 (1H, d, J = 8.4 Hz), 7.25 (1H, d, J = 6.8 Hz), 7.28(1H, d, J = 6.6 Hz), 7.40 (1H, td, J = 8.2 Hz, J = 2.2 Hz), 7.52 (1H, td, J = 6.4 Hz, J = 2.1 Hz), 7.61 (1H, td, J = 6.6 Hz, J = 1.6 Hz), 8.07 (1H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 61.2, 105.5, 121.3, 128.4, 128.5, 128.9, 131.4, 133.2, 137.7, 140.1, 140.3, 162.5, 164.8; HRMS calcd for $C_{14}H_{13}NO_3$ 243.0895, found 243.0889.

Butyl 2-(2-oxo-1,2-dihydro-1-pyridinyl)benzoate (3i): syrupy liquid; IR (neat) 3021, 1722, 1665; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (3H, t, J = 7.2 Hz), 1.22−1.28 (2H, m), 1.45−1.48 (2H, m), 4.08 (2H, t, J = 6.8 Hz), 6.21 (1H, td, J = 6.8 Hz, J = 1.2 Hz), 6.59 (1H, d, J = 9.2 Hz), 7.18 (1H, d, J = 6.8 Hz), 7.22 (1H, d, J = 7.2 Hz), 7.36 (1H, ddd, J = 9.2 Hz, J = 6.4 Hz, J = 1.6 Hz), 7.47 (1H, td, J = 7.6 Hz, J = 2.2 Hz), 7.59 (1H, td, J = 7.2 Hz, J = 2.0 Hz), 8.03 (1H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 19.0, 30.3, 65.3, 105.5, 121.5, 126.4, 128.5, 128.9, 131.5, 133.2, 137.7, 140.1, 140.3, 162.5, 164.9; HRMS calcd for $C_{16}H_{17}NO_3$ 271.1209, found 271.1211.

Isobutyl 2-(2-oxo-1,2-dihydro-1-pyridinyl)benzoate (3j): mp = 63 °C; IR (KBr) 3029, 1721, 1674; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (6H, dd, J = 6.6 Hz, J = 4.0 Hz), 1.79−1.88 (1H, m), 3.92 (2H, d, J = 6.8 Hz), 6.21 (1H, td, J = 6.4 Hz, J = 1.1 Hz), 6.58 (1H, dt, J = 9.3 Hz, J = 1.0 Hz), 7.23 (2H, td, J = 6.4 Hz, J = 1.3 Hz), 7.38(1H, ddd, J = 9.2 Hz, J = 6.5 Hz, J = 2.0 Hz), 7.49 (1H, td, J = 7.8 Hz, J = 1.5 Hz), 7.62 (1H, td, J = 7.6 Hz, J = 1.7 Hz), 8.06 (1H, dd, J = 7.8 Hz, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 27.5, 71.5, 105.5, 121.5, 121.5, 128.5, 128.9, 129.2, 131.4, 133.2, 137.7, 140.0, 140.4, 162.4, 164.8; HRMS calcd for $C_{16}H_{17}NO_3$ 271.1209, found 271.1201.

1-(2-Acetyl-3-methylphenyl)-1,2-dihydro-2-pyridone (6a): mp = 108−110 °C; IR (KBr) 3014, 1675, 1653; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.31 (3H, s), 2.32 (3H, s) 6.16 (1H, td, J = 6.6 Hz, J = 1.2 Hz), 6.53 (1H, d, J = 9.2 Hz), 7.05 (1H, d, J = 7.7 Hz), 7.14 (1H, d, J = 6.6 Hz), 7.24 (1H, d, J = 7.7 Hz), 7.34 (2H, t, J = 7.5 Hz), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 30.8, 105.7, 121.3, 125.1, 129.7, 131.0, 134.6, 136.7, 138.5, 139.7, 140.3, 162.1, 204.1; HRMS calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0943.

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **3a**−**j** and **6a** and ORTEP plots and X-ray data of compounds **3g** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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