Enolate Ions as β-Activators of Ortho-Metalation: Direct Synthesis of 3-Aminoindenones

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β-Ketonitriles derived from a Claisen condensation of benzoate esters with alkyl- or phenylacetonitriles lead to 3-aminoindenones in the presence of excess LDA. This new reaction is also applicable to pyridine carboxylic esters. All of the 3-aminoindenones and their aza analogues can be hydrolyzed by acid to give the corresponding 1,3-indandiones. The mechanism of the reaction falls into the directed-ortho-metalation class in which the initial enolate ion of the keto-nitrile directs self-metalation at an ortho position. The new anion then cyclizes onto the nitrile group to generate an aminoindenone. Surprisingly the simplest member of the series, benzoylacetonitrile, does not undergo cyclization. Mechanistic isotope studies revealed that this substance preferentially and directly forms a dianion on the side chain, which is not further deprotonated at the ortho position of the aromatic ring.

Introduction

A large variety of aromatic substituents will direct metalation at an unsubstituted adjacent position of an aryl ring. These fall directly into two classes: (a) those that are strongly electron withdrawing (α-activators) and (b) those that form a strong coordination complex with the metal ion (β-activators).[1] Some substituents possess both characteristics.

Although in principle simple enolate anions might be expected to fall into the β-activator class by analogy with the very useful anions of secondary amides,[2] such is not the case. In a significant study on the enolate anions of a series of acetophenones, Klein and Medlik-Balan[3] found that polymetalation tended to dominate, and because of this, the use of such enolate anions appeared to have little synthetic value. However, in contrast to these simple enolates, we have now found that the monoanion of a 2-cyanoacetophenone undergoes lithiation by LDA at the ortho-position and that the resulting new anion subsequently attacks the cyano group in an unusual cyclization reaction to give a 3-amino-indenone.[4]

This discovery was quite fortuitous and was the result of an attempt to condense 4-methoxyphenylacetonitrile with methyl 4-methoxybenzoate, using an excess of LDA as the base. The reaction mixture instead of remaining essentially colorless as might be expected for a simple Claisen-type condensation, developed a brilliant red color. It was this observation that led us to investigate the reaction further. We have now explored the scope of this reaction and have found that beyond the original report it can be applied to pyridine carboxylic esters also. As a method of synthesis of this class of substance it is quite versatile.

The only previously known method[5] for the synthesis of 3-amino-indenones requires several steps and gives low overall yields. Acid hydrolysis of the 3-amino-indenones afforded the corresponding 1,3-indandiones which are known to have a wide spectrum of biological activity,[6] including thrombolytic properties, and have been used as rodenticides.

Results and Discussion

The overall process that converts the initial condensation product **3** to the 3-aminoindenones **7** is shown in Scheme 1. This new reaction appears to be general in scope. However when the condensation is performed in one pot, the yields are poor to modest due to preferential attack of the LDA on the benzoate ester to give an *N*,*N*-diisopropylamide. The latter was always a significant product under these conditions. Prior synthesis of the keto-nitrile **3** using sodium hydride as the base followed by treatment with LDA in a separate reaction (two-pot sequence) leads to a substantial increase in the yield of **7**.

Table 1 summarizes the results obtained with the aryl esters **1** and a variety of acetonitriles **2**. The reactions were optimized only with regard to LDA (4−6 equiv). Generally ethyl esters were used because they gave less of the *N*,*N*-diisopropylamide byproduct than the methyl esters. No other byproducts apart from the amide are formed. In no case in this series was the reaction complicated by lithiation of the aryl ring derived from the acetonitrile even when methoxy groups were present.

Entry 1 represents the first case that was discovered whereas entries 2−5, 7−13, are examples which demonstrate the generality of this reaction. In the case of entry 6, it might have been expected that the intermediate ortho anion would preferentially have eliminated the

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(6) (a) Horeau, A.; Jacques, J. *Bull. Soc. Chim. Fr.* **1984**, 53. (b) Jacques, L. B.; Gordon, E.; Lapp, E. *Can. Med. Assoc. J.* **1950**, *62*, 465. (c) Blaustein, A. *Ibid.* **1950**, *62*, 470.

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Scheme 1

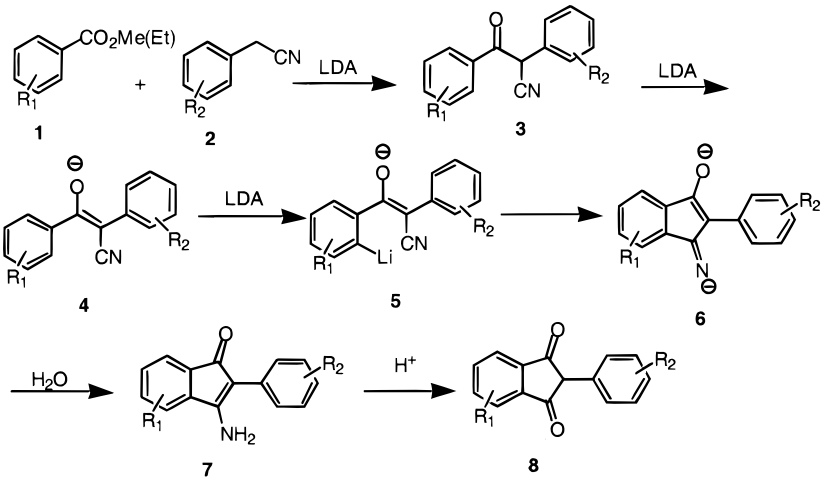
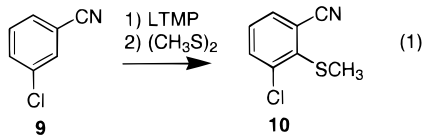


Table 1. 3-Aminoindenones (7) Obtained by the One-Stage Process and the Two-Pot Sequence and the 1,3-indandione (8) Products of Hydrolysis

entry	R_1 substituents	R_2 substituents	yield by one-stage process (%)	yield by two-pot sequence (%)	yield of 1,3-indandione (%)
1	4-OMe	4-OMe	57	59	65
2	H	4-OMe	57	56	76
3	4-OMe	2-OMe	15	69	81
4	H	2-OMe	10	43	
5	3-OMe	4-OMe	28		
6	3-Cl	4-OMe	33	56	60
7	4-OMe	H	15	56	74
8	H	H	13	48	
9	2-OMe	4-OMe	8	45	
10	4-OMe	3-OMe	8		
11	H	3-OMe		51	
12	4-OMe	3,4-dimethoxy	27		
13	3,4,5-trimethoxy	4-OMe	45		8

chlorine atom at the 3-position in a benzyne reaction. However cyclization seems to take precedence, and there is a parallel case in that *m*-chlorobenzonitrile (**9**), on treatment with lithium tetramethyl piperidide (LTMP) followed by dimethyl disulfide, gives 2-chloro-4-cyanothioanisole (**10**) rather than undergoing an elimination reaction[7] (eq 1). In the case of entries 5 and 6, the ortho-lithiation occurs at the 2 position. The methoxy group, being a directed-metalation group situated meta to the enolate ion, contributes to ortho-lithiation between the two groups. The chlorine atom makes the 2 position more acidic by inductive effects.

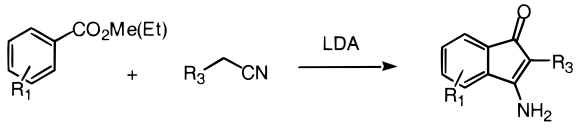


We also have found that the reaction proceeds with most alkylacetonitriles, 3-pyridylacetonitrile, phenylthioacetonitrile, and malononitrile. Table 2 summarizes the results obtained with these acetonitriles.

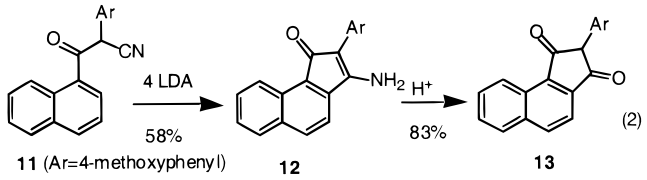
On the aromatic ester side the reaction proved extendable to the naphthalene and pyridine series. When keto nitrile **11**, obtained by the condensation of **2** (R_2 = 4-OMe) with methyl 1-naphthoate, was subjected to the cyclization conditions, a single product **12** was obtained in 41% overall yield (one-stage process 22% yield). Cyclization at the 8-position, which might be a competing process, was not observed. Acid hydrolysis of **12** led to **13** (eq 2).

(7) See ref 24 in ref 1, p 54.

Table 2. 3-Aminoindenones Obtained from Various Functionalized Nitriles

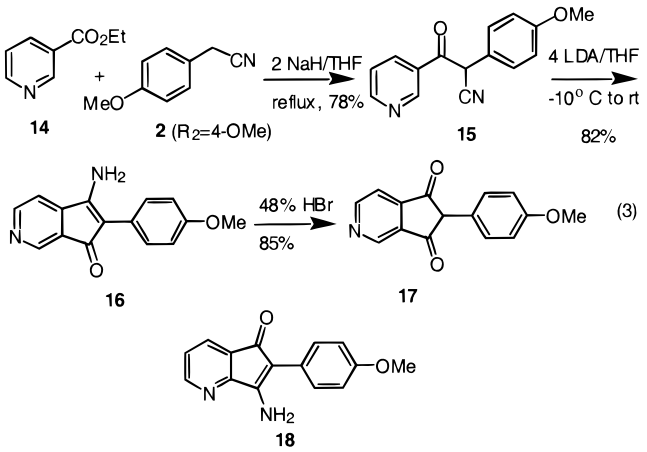


entry	R_1	R_3	yield by one-stage process (%)	yield by two-pot sequence (%)
1	H	CH_3	83	
2	4-OMe	CH_2CH_3		49
3	H	−SPh	17	
4	H	CN		13
5	H	3-pyridyl		28
6	H	H	0	0



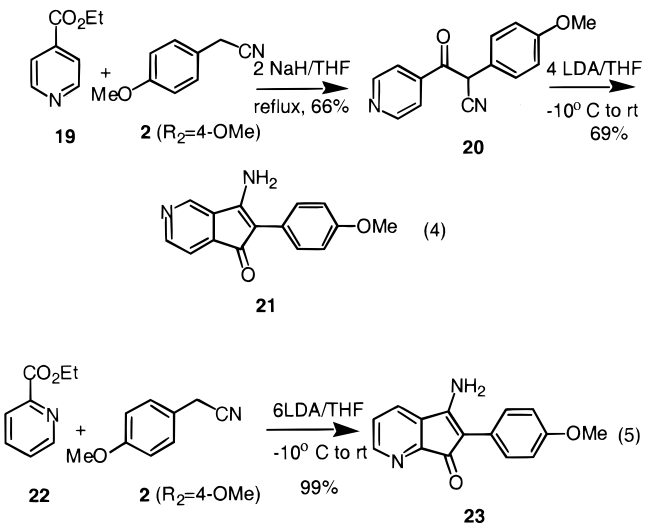
In the pyridine series, condensation of ethyl nicotinate (**14**) with **2** (R_1 = 4-OMe) in the presence of sodium hydride led to the keto nitrile **15**. The latter when subjected to an excess of LDA afforded the cyclic product **16** as the unique product. No material derived from lithiation at the 2-position of the pyridine ring could be detected. That reaction had occurred at the 4-position of the pyridine ring was evident from the ^{1}H NMR data. A low-field singlet peak is observed in the spectrum of **15** at 8.4 ppm, which is assigned to the hydrogen atom at the 2-position. The alternate structure **18** might be expected to show three multiplets each for a single hydrogen. Hydrolysis of **16** then led in good yield to compound **17**, the first member of compounds having this type of structure to be reported. The deprotonation at the 4-position of the pyridine ring is in accord with various reports in the literature, which demonstrate than an ortho-directing metalation group at the 3-position undergoes lithiation at the 4-position.[8] It is possible that

the pair of electrons on the nitrogen atom discourage the anion formation at the 2-position because of the electrostatic repulsion.



(3)

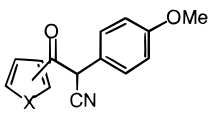
In a similar two-pot sequence ethyl isonicotinate (**19**), when allowed to react with **2** (R_2 = 4-OMe), gave **21** in overall 46% yield, whereas the one-stage process failed completely (eq 4). By contrast and remarkably, the one-stage procedure utilizing ethyl picolinate (**22**) led to **23** in 99% yield (eq 5).



(4)

(5)

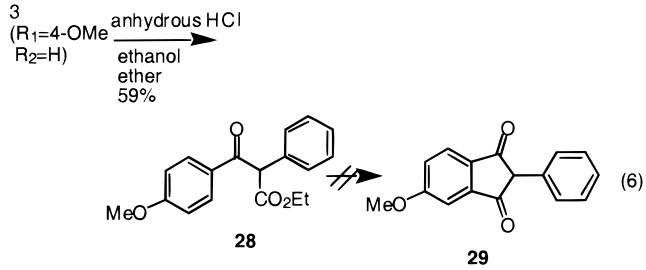
Attempts to extend this type of cyclization reaction to five membered aromatic systems met with no success. Intermediates **24**, derived respectively from ethyl 2-furoate, ethyl 3-furoate or ethyl thiophene 2-carboxylate and 4-methoxyphenylacetonitrile (2; R_2 = 4-OMe), when treated individually with excess LDA did not give any of the desired product. In all cases needless to say the one-stage procedure failed also.



24-26 (X=O, S)

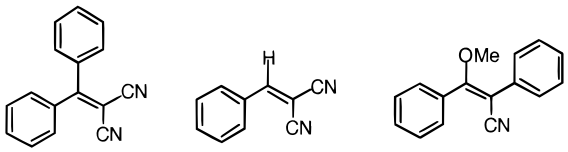
The feasibility of utilizing bases other than LDA was also examined. When 2,3-diphenyl-3-oxo-propionitrile (**3**; R_1 = H, R_2 = H) was treated with *n*-BuLi, only a trace amount of the corresponding 3-amino-indenone was obtained. The major product after hydrolysis was ketone **27** ($PhCOCHPhCO(CH_2)_3CH_3$), arising from the addition of *n*-BuLi to the nitrile. However when the same keto-nitrile was treated with *t*-BuLi, the corresponding 3-amino-indenone was obtained in a yield (48%) similar to what was obtained with LDA.

By analogy to the cyclization of β-keto-nitriles to form 3-amino-indenones, we also examined the possibility that β-keto-esters might cyclize directly to 1,3-indandiones in the presence of excess LDA. When the β-keto-ester **28** was synthesized from the corresponding β-keto-nitrile and treated with excess of LDA, only starting material was recovered after workup (eq 6). It appears that in the case of β-keto-esters complete delocalization of negative charge across both the keto and the ester carbonyls may prevent cyclization. However we did not determine if deprotonation was in fact occurring at the position ortho to the keto group.



(6)

Nevertheless, in investigating the mechanistic aspects of the deprotonation process, we did examine several substances related to **3**, namely **30**−**32**. These were selected in order to determine if the vinylogous nitrile (a possible α-activator) was responsible for the lithiation or if it was due simply to the enolate anion (β-activator). In any event, treatment of **32** with LDA at −78 °C led to a complicated mixture of products from which no sensible information could be derived. On the other hand LDA treatment of **30** and **31** did not effect lithiation. This is surprising because benzonitrile is lithiated at the ortho position by this reagent.[9]



The lack of cyclization of benzoylacetonitrile, which was formed from acetonitrile and ethyl benzoate (entry 6 in Table 2) in the presence of LDA, was perplexing. Even in the presence of *t*-BuLi, starting material was recovered after workup, no matter what conditions were employed. It was not even clear if the corresponding ortho-lithiated species was being formed. To test this, an attempt was made to trap the putative aromatic anion with TMSCl. However, subsequent aqueous workup followed by ^{1}H NMR failed to reveal any TMS group on the aromatic ring.

(8) Watanabe, M.; Shinoda, E.; Shimizu, Y.; Furukawa, S.; Iwao, M.; Kuraishi, T. *Tetrahedron* **1987**, *43*, 5281.

(9) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

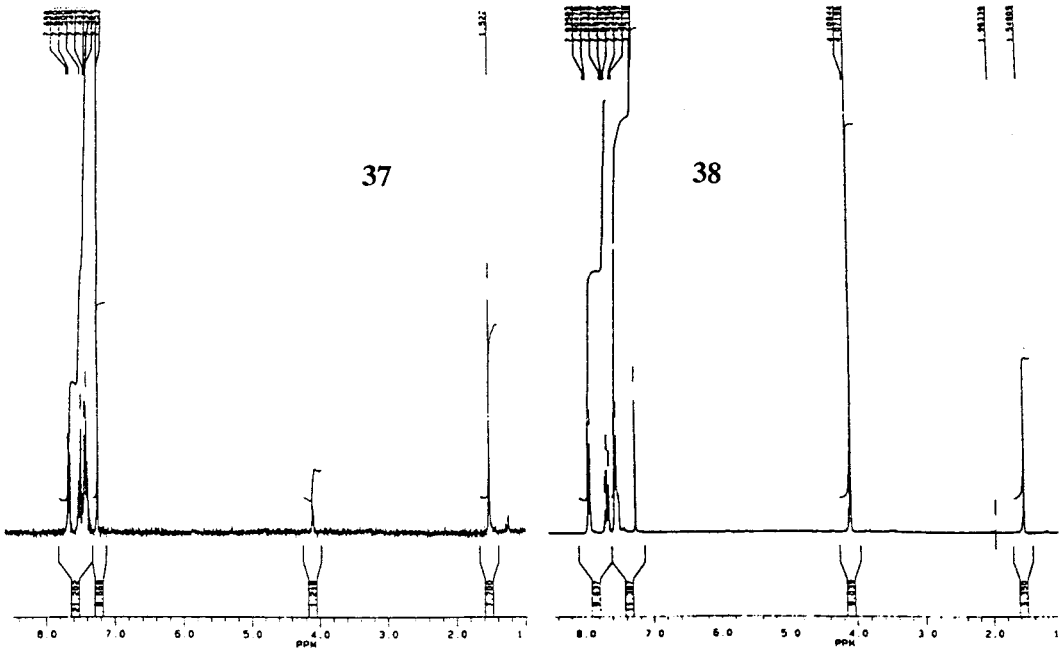
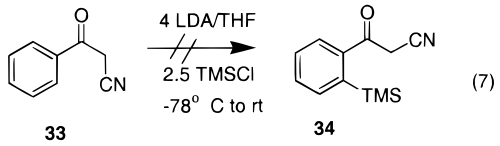


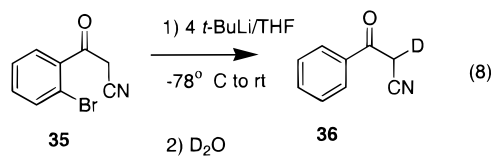
Figure 1. ^{1}H NMR spectra of **37** and **38**.

We originally had thought that the corresponding enolate would adopt a geometry in which the phenyl and the cyano group would be in a trans relationship, thus making it impossible for an ortho anion to cyclize. Again when we carried out the cyclization in the presence of HMPA, which is known to equilibrate the cis and trans isomers of enolate ions,[10] still no cyclization was observed (eq 7).



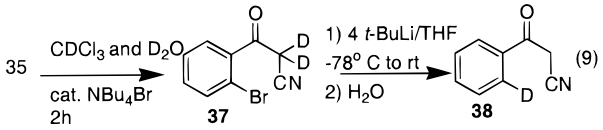
To generate the desired dianion in a controlled way, 2-bromobenzoylacetonitrile was treated with an excess of *t*-BuLi. It was expected that under these conditions of metal−halogen exchange, cyclization with the nitrile group would occur. However, again after workup, only benzoylacetonitrile was obtained!

In an attempt to determine the fate of the *o*-anion in this case, the reaction was repeated but quenched with D_2O. To our surprise, deuterium incorporation was observed only on the side chain. Only one deuterium was seen in the side chain because the D_2O quenches only the carbanion but not the oxyanion (see **40** below). Further treatment with aqueous HCl then protonates the latter anion, precipitating the keto-nitrile with only one deuterium at the α-position. Importantly, no deuteration had occurred on the phenyl ring, as was evident from the ^{1}H NMR spectrum of the product (eq 8).



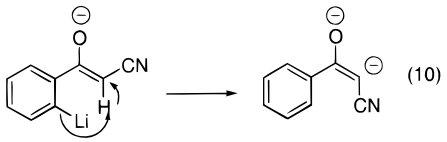
(10) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

From this result, it had to be concluded that the anion derived from the metal−halogen exchange reaction removes a proton from the side chain, thus creating a dianion at this location. To test this hypothesis, the dideuterated benzoylacetonitrile **37** was synthesized and treated with *t*-BuLi. The product after aqueous workup clearly showed D incorporation on the phenyl ring (eq 9), as was evident from the NMR data.



In the NMR spectrum of 2-bromobenzoylacetonitrile, a singlet appears at 4.07 ppm (2H) which is essentially absent in the deuterated form **37**. After treatment with *t*-BuLi followed by aqueous workup, the singlet at 4.07 ppm reappears, but by contrast with benzoylacetonitrile itself, one of the ortho protons is missing from the spectrum of **38**. In addition the mass spectrum of **38** showed a parent ion peak at m/z=146.

The simplest explanation of these facts is that after the initial formation of the ortho anion, the latter immediately abstracts a proton from the side chain in an internal transfer process. This implies that dianion **39** is less stable than dianion **40** (eq 10). This now explains why benzoylacetonitrile fails to cyclize. In this case, direct deprotonation of the second proton of the side chain occurs without the intermediacy of an ortho aryl anion. This was confirmed by the fact that when **38** was treated with either LDA or *t*-BuLi, no loss of deuterium from the phenyl ring was observed. Thus it now appears clear that the dianion represented by **39** surprisingly is thermodynamically less stable than the dianion **40**, in which both charges are on the side chain. This now offers a complete explanation as to why the cyclization of benzoylacetonitrile could not be effected (Figure 1).



39 40

Conclusions

Past investigations[3] of the enolate anions of alkyl aryl ketones have revealed little in the way of useful further ortho metalation despite the fact that by analogy with the enolate anions of *N*-alkyl aromatic amides they might be expected to exert a *β*-activation effect. Current studies now show that when a cyano group is introduced on the alkyl group α to the carbonyl, *β*-activation of the ortho position of the aromatic ring occurs smoothly under the influence of LDA or *t*-BuLi. The resulting ortho anionic species attacks the internal nitrile group and the end product of the reaction sequence is a 3-aminoindenone. The reaction is also applicable to the analogous pyridine compounds.

Surprisingly benzoylacetonitrile does not give a cyclic product but instead undergoes a double deprotonation on the side chain. Attempts to generate the needed dianion from 2-bromobenzoylacetonitrile reveal, via isotopic studies, a novel internal proton transfer. From this can be concluded that the side chain dilithio species is thermodynamically more stable than the dilithio intermediate in which one lithium is on the aromatic ring (ortho) and the other is on the side chain.

Experimental Section

General Methods. Lithium diisopropyl amide (LDA), as a 2.0 M solution in THF and ethyl benzene, *n*-BuLi as a 2.0 M solution in cyclohexane, *t*-BuLi as a 1.7 M solution in pentane, and sodium hydride (60% dispersion in mineral oil) were purchased from commercial sources.

NMR spectra were recorded on both 250 and 300 MHz spectrometers. Melting points are uncorrected. Molecular weights were recorded on an electron impact mass spectrometer. All compounds were judged pure by TLC (single spot) in two solvent systems: 1/1 ethyl acetate−hexane and 95/5 dichloromethane−methanol

One-Stage Reaction. LDA (6 equiv relative to the nitrile and ester) was added to a three-necked rounded-bottomed flask equipped with a thermometer and a magnetic bar at −10 °C. The reagents were dissolved in THF and added slowly to LDA. The mixture was left to stir until it reached room temperature. When the reaction was complete as judged by TLC (all reactions were run overnight unless otherwise mentioned), a precipitate will be seen in the dark-colored mixture. Water was then added, and the bulk of THF was removed by reduced pressure. The resulting slurry was filtered and the collected solid was washed with more water and dried under vacuum over phosphorus pentoxide. Recrystallization from 2-propanol then gave the pure 3-aminoindenone. For entry numbers refer to Tables 1 and 2.

3-Amino-2-(4-methoxyphenyl)-5-methoxy-1-indenone (Table 1, Entry 1). From 1.23 g of methyl 4-methoxybenzoate (7.40 mmol), 1.08 g of 4-methoxyphenylacetonitrile (7.37 mmol), and 22.0 mL LDA (44.0 mmol) was obtained 1.18 g of the 3-aminoindenone (57%). Mp: 220−221 °C. δ ^{1}H NMR (DMSO-d_6): 3.76 (3H, s); 3.81 (3H, s); 6.79 (1H, d, J = 7.80 Hz); 6.94 (2H, d, J = 8.55 Hz); 7.21 (1H, d, J = 7.86 Hz); 7.39 (2H, s); 7.43 (1H, s); 7.73 (2H, br). δ ^{13}C NMR (DMSO-d_6): 55.0; 55.6; 103.7; 107.4; 112.0; 113.7; 120.7; 125.3; 127.1; 129.2; 141.0; 156.8; 159.4; 162.3; 190.0. MS: M^+ = 281. HRMS: calcd for $C_{17}H_{15}NO_3$ 281.1052, found 281.1047

3-Amino-2-(4-methoxyphenyl)-1-indenone (Table 1, Entry 2). From 1.00 g of methyl benzoate (7.34 mmol), 1.08 g of 4-methoxyphenylacetonitrile (7.47 mmol), and 22.0 mL of LDA (44.0 mmol) was obtained 1.07 g of the 3-aminoindenone (57%). Mp: 264−265 °C. δ ^{1}H NMR (DMSO-d_6): 3.76 (3H, s); 6.95 (2H, d, J = 8.43 Hz); 7.26−7.44 (5H, m); 7.68 (1H, d, J = 6.80 Hz); 7.93 (2H, br). δ ^{13}C NMR (DMSO-d_6): 55.0; 104.7; 113.7; 118.6; 119.3; 125.2; 129.3; 130.1; 131.1; 135.1; 138.5; 156.9; 161.2; 190.0. MS: M^+ = 251. HRMS: calcd for $C_{16}H_{13}NO_2$ 251.0946, found 251.0951.

3-Amino-2-(2-methoxyphenyl)-5-methoxy-1-indenone (Table 1, Entry 3). From 1.13 g of methyl 4-methoxybenzoate (6.80 mmol), 1.00 g of 2-methoxyphenylacetonitrile (6.79 mmol), and 21.0 mL of LDA (42.0 mmol) was obtained 0.240 g of the 3-aminoindenone (15%). Mp: 196.5−197.5 °C. δ ^{1}H NMR (DMSO-d_6): 3.76 (3H, s); 3.82 (3H, s); 6.80 (1H, d, J = 9.74 Hz); 6.82−7.02 (2H, m); 7.19−7.26 (3H, m); 7.36 (1H, s); 7.82 (br). δ ^{13}C NMR (DMSO-d_6): 54.9; 55.6; 102.1; 107.3; 111.0; 111.9; 120.8; 121.2; 127.2; 128.0; 131.7; 141.1; 156.5; 160.2; 162.2; 189.6. MS: M^+ = 281; HRMS: calcd for $C_{17}H_{15}NO_3$ 281.1052, found 281.1042.

3-Amino-2-(2-methoxyphenyl)-1-indenone (Table 1, Entry 4). From 0.880 g of methyl benzoate (6.46 mmol), 0.950 g of 2-methoxyphenylacetonitrile (6.45 mmol), and 9.60 mL of LDA (19.2 mmol) was obtained 0.160 g of the 3-aminoindenone (10%). Mp: 160−162 °C. δ ^{1}H NMR (DMSO-d_6): 3.76 (3H, s); 6.92−7.03 (2H, m); 7.21−7.43 (5H, m); 7.64 (1H, d, J = 6.67 Hz); 8.04 (2H, br). δ ^{13}C NMR (DMSO-d_6): 54.9; 101.5; 111.0; 118.4; 119.3; 119.8; 121.0; 127.3; 130.0; 130.8; 131.7; 136.8; 138.4; 156.5; 161.7; 188.8. MS: M^+ = 251. HRMS: calcd for $C_{16}H_{13}NO_2$ 251.0946, found 251.0943

3-Amino-2-(4-methoxyphenyl)-4-methoxy-1-indenone (Table 1, Entry 5). From 0.800 g of ethyl 3-methoxybenzoate (4.44 mmol), 0.650 g of 4-methoxyphenylacetonitrile (4.42 mmol), and 10.0 mL of LDA (20.0 mmol), after 2 h of reaction time, was obtained 0.350 g of the 3-aminoindenone (28%). Mp: 189.5−190.5 °C. δ ^{1}H NMR (DMSO-d_6): 3.76 (3H, s); 3.93 (3H, s); 6.95 (3H, dd, J = 11.31 Hz, J = 4.18 Hz); 7.16 (1H, d, J = 8.43 Hz); 7.37 (3H, dd, J = 12.88 Hz; J = 2.43 Hz); 7.82 (br). δ ^{13}C NMR (DMSO-d_6): 55.9; 56.0; 103.5; 113.0; 113.7; 116.4; 121.8; 125.0; 129.1; 132.5; 136.9; 153.3; 156.7; 162.1; 189.5. MS: M^+ = 281. HRMS calcd for $C_{17}H_{15}NO_3$ 281.1052, found 281.1047.

3-Amino-2-(4-methoxyphenyl)-4-chloro-1-indenone (Table 1, Entry 6). From 1.26 g of methyl 3-chlorobenzoate (7.39 mmol), 1.09 g of 4-methoxyphenylacetonitrile (7.41 mmol), and 22.1 mL of LDA (44.2 mmol), after 1 h of reaction time, was obtained 0.700 g of the 3-aminoindenone (33%). Mp: 198−199 °C. δ ^{1}H NMR (DMSO-d_6): 3.77 (3H, s); 6.97 (2H, d, J = 8.73 Hz); 7.28−7.41 (5H, m). δ ^{13}C NMR (DMSO-d_6): 55.1; 104.1; 113.8; 118.8; 123.8; 125.0; 129.8; 132.4; 133.0; 137.4; 157.3; 160.4; 188.9. MS: M^+ = 285, 83.6 for Cl = 35. MS: M^+ = 287, 32.3 for Cl = 37. HRMS: calcd for $C_{16}H_{12}NO_2{}^{35}Cl$ 285.0556, found 285.0545.

3-Amino-2-phenyl-5-methoxy-1-indenone (Table 1, Entry 7). From 1.38 g of methyl 4-methoxybenzoate (8.30 mmol), 0.970 g of phenylacetonitrile (8.28 mmol), and 25.0 mL of LDA (50.0 mmol) was obtained 0.320 g of the 3-aminoindenone (15%). Mp: 220−222 °C. δ ^{1}H NMR (DMSO-d_6): 3.82 (3H, s); 6.83 (1H, dd, J = 9.64 Hz, J = 6.18 Hz); 7.13−7.52 (7H, m); 7.82 (2H, br). δ ^{13}C NMR (DMSO-d_6): 55.6; 103.7; 107.5; 120.9; 124.8; 127.1; 128.0; 128.1; 133.1; 140.9; 160.1; 162.4; 189.9. MS: M^+ = 251. HRMS: calcd for $C_{16}H_{13}NO_2$ 251.0946, found 251.0945.

3-Amino-2-phenyl-1-indenone (Table 1, Entry 8). From 1.13 g of methyl benzoate (8.31 mmol), 0.970 g of phenylacetonitrile (8.28 mmol), and 25.0 mL of LDA (50.0 mmol) was obtained 0.242 g of the 3-amino-indenone (13%). Mp: 266−268 °C. δ ^{1}H NMR (DMSO-d_6): 7.16 (1H, t, J = 14.6 Hz); 7.31−7.53 (7H, m); 7.72 (1H, d, J = 6.65 Hz). δ ^{13}C NMR (DMSO-d_6): 103.2; 118.7; 119.4; 124.8; 126.1; 126.2; 130.4; 131.1; 132.9; 138.2; 161.8; 189.8. MS: M^+ = 221. HRMS: calcd for $C_{15}H_{11}NO$ 221.0841, found 221.0831.

3-Amino-2-(4-methoxyphenyl)-7-methoxy-1-indenone (Table 1, Entry 9). From 1.22 g of methyl 2-methoxybenzoate

(7.34 mmol), 1.09 g of 4-methoxyphenylacetonitrile (7.41 mmol), and 22.1 mL of LDA (44.2 mmol) was obtained 0.171 g of the 3-aminoindenone (8%). Mp: 184−186 °C. δ ^{1}H NMR (DMSO-d_6): 3.76 (3H, s); 3.83 (3H, s); 6.94 (2H, d, J = 8.79 Hz); 7.05 (1H, d, J = 8.14 Hz); 7.31−7.42 (4H, m); 7.58 (2H, br). δ ^{13}C NMR (DMSO-d_6): 55.0; 55.7; 104.2; 111.7; 113.6; 116.2; 118.0; 125.3; 129.3; 132.9; 141.0; 154.1; 156.0; 159.0; 189.5. MS: M^+ = 281. HRMS: calcd for $C_{17}H_{15}NO_3$ 281.1052, found 281.1057.

3-Amino-2-(3-methoxyphenyl)-5-methoxy-1-indenone (Table 1, Entry 10). From 1.25 g of methyl 4-methoxybenzoate (7.52 mmol), 1.05 g of 3-methoxyphenylacetonitrile (7.13 mmol), and 14.3 mL of LDA (28.6 mmol) there was obtained 0.152 g of the 3-amino-indenone (7.5%). Mp: 250−251 °C. δ ^{1}H NMR (DMSO-d_6): 3.78 (3H, s); 3.83 (3H, s); 6.74 (1H, d, J = 7.77 Hz); 6.83 (1H, d, J = 2.09 Hz); 7.08 (2H, s); 7.23−7.31 (2H, m); 7.44 (1H, s); 7.84 (2H, br). δ ^{13}C NMR (DMSO-d_6): 54.8; 55.8; 103.8; 107.5; 110.5; 112.4; 113.3; 120.3; 120.9; 127.5; 129.1; 134.3; 141.6; 159.8; 160.2; 189.8. MS: M^+ = 281. HRMS: calcd for $C_{17}H_{15}NO_3$ 281.1052, found 281.1041.

3-Amino-2-(3,4-dimethoxyphenyl)-5-methoxy-1-indenone (Table 1, Entry 12). From 1.88 g of methyl 4-methoxybenzoate (11.3 mmol), 2.04 g of 3,4-dimethoxyphenylacetonitrile (11.5 mmol), and 34.0 mL of LDA (68.0 mmol) there was obtained 0.973 g of the 3-aminoindenone (27%). Mp: 270−272 °C. δ ^{1}H NMR (DMSO-d_6): 3.78 (3H, s); 3.81 (3H, s); 3.92 (3H, s); 6.78 (1H, d, J = 1.80 Hz); 6.82 (2H, s); 7.08 (1H, s); 7.22 (1H, d, J = 7.85 Hz); 7.39 (1H, s); 7.77 (2H, br). δ ^{13}C NMR (DMSO-d_6): 55.2; 55.6; 103.9; 107.4; 112.0; 120.4; 120.6; 125.7; 127.1; 141.0; 146.5; 148.4; 159.5; 162.3; 188.6. MS: M^+ = 311; HRMS: calcd for $C_{18}H_{17}NO_4$ 311.1157, found 311.1162.

3-Amino-2-(4-methoxyphenyl)-4,5,6-trimethoxy-1-indenone (Table 1, Entry 13). From 3.40 g of methyl 3,4,5-trimethoxybenzoate (15.0 mmol), 2.17 g of 4-methoxyphenylacetonitrile (14.7 mmol), and 44.3 mL of LDA (88.6 mmol) there was obtained 2.36 g of the 3-aminoindenone (45%). Mp: 182−184 °C. δ ^{1}H NMR (DMSO-d_6): 3.76 (3H, s); 3.80 (3H, s); 3.88 (3H, s); 3.99 (3H, s); 6.89 (1H, s); 6.95 (2H, d, J = 8.57 Hz); 7.37 (2H, d, J = 8.59 Hz). δ ^{13}C NMR (DMSO-d_6): 55.0; 56.4; 60.5; 61.4; 101.9; 113.7; 119.6; 125.0; 129.0; 131.4; 143.7; 148.3; 156.7; 157.5; 161.5; 189.1. MS: M^+ = 341. HRMS: calcd for $C_{19}H_{19}NO_5$ 341.1250, found 341.1256.

3-Amino-2-methyl-1-indenone (Table 2, Entry 1). From 1.05 g of ethyl benzoate (7.00 mmol), 0.380 g of propionitrile (6.91 mmol), and 21.0 mL of LDA (42.0 mmol) there was obtained 0.910 g of the 3-aminoindenone (83%). Mp: 222−223 °C. δ ^{1}H NMR (DMSO-d_6): 1.56 (3H, s); 7.14 (1H, d, J = 6.92 Hz); 7.21−7.33 (2H, m); 7.43 (1H, d, J = 4.38 Hz); 7.53 (2H, br). δ ^{13}C NMR (DMSO-d_6): 6.0; 99.2; 117.5; 129.3; 130.3; 135.8; 138.8; 162.5; 191.4. MS: M^+ = 159. HRMS: calcd for $C_{10}H_9NO$ 159.0684, found 159.0689.

3-Amino-2-ethyl-5-methoxy-1-indenone (Table 2, Entry 2). From 1.93 g of methyl 4-methoxybenzoate (11.6 mmol), 0.790 g of butyronitrile (11.5 mmol), and 34.5 mL of LDA (69.0 mmol) there was obtained 1.05 g of the 3-aminoindenone (49%). Mp: 205−207 °C. δ ^{1}H NMR (DMSO-d_6): 0.93 (3H, t, J = 14.8 Hz); 2.13 (2H, quadruplet; J = 17.2 Hz); 3.77 (3H, s); 6.68 (1H, dd, J = 9.87 Hz; J = 5.72 Hz); 7.07 (1H, d, J = 3.80 Hz); 7.15 (1H, s); 7.42 (2H, br). δ ^{13}C NMR (DMSO-d_6): 15.6; 16.0; 55.5; 106.3; 109.0; 110.6; 119.8; 127.7; 141.4; 160.0; 161.9; 191.1. MS: M^+ = 203; HRMS: calcd for $C_{12}H_{13}NO_2$ 203.0946, found 203.0943.

3-Amino-2-thiophenyl-5-1-indenone (Table 2, Entry 3). From 1.06 g of phenylthioacetonitrile (7.11 mmol), 1.07 g of ethyl benzoate (7.13 mmol), and 14.3 mL of LDA (28.6 mmol) there was obtained 0.300 g of the 3-aminoindenone (17%). Mp: 190−191 °C. δ ^{1}H NMR (DMSO-d_6): 7.07 (3H, dd, J = 9.00 Hz; J = 6.30 Hz); 7.22 (2H, t, J = 15.3 Hz); 7.40 (1H, m); 7.48−7.51 (2H, m); 7.78 (1H, dd, J = 8.40 Hz; J = 4.80 Hz). δ ^{13}C NMR (DMSO-d_6): 88.3; 119.8; 120.0; 124.6; 125.0; 128.8; 131.3; 131.4; 135.7; 136.7; 138.6; 169.8; 189.0. MS: M^+ = 253. HRMS: calcd for $C_{15}H_{11}NOS$ 253.0561, found 253.0563.

3-Amino-2-(4-methoxyphenyl)-1-[benz][*e*]-1-indenone (12). From 1.50 g of 1-ethylnaphthoate (7.50 mmol), 1.08 g of 4-methoxyphenylacetonitrile (7.37 mmol), and 22.0 mL of LDA (44.0 mmol) there was obtained 0.510 g of the cyclized product (22%). Mp: 284−287 °C. δ ^{1}H NMR (DMSO-d_6): 3.76 (3H, s); 6.97 (2H, d, J = 8.50 Hz); 7.42−7.51 (2H, m); 7.85−8.02 (5H, m); 8.82−8.85 (1H, d, J = 8.36 Hz). MS: M^+=301; HRMS: calcd for $C_{20}H_{15}NO_2$ 301.1103, found 301.1099

5-Amino-6-(4-methoxyphenyl)-2-pyrindin-7-one (16). From 1.14 g of ethyl nicotinate (7.35 mmol), 1.08 g of 4-methoxyphenylacetonitrile (7.37 mmol), and 44.3 mL of LDA (88.6 mmol) was obtained 0.610 g of the cyclized product (33%). Mp: 263.5−264.5 °C. δ ^{1}H NMR (DMSO-d_6): 3.78 (3H, s); 6.99 (2H, d, J = 8.65 Hz); 7.44 (2H, d, J = 8.68 Hz); 7.70 (1H, d, J = 4.63 Hz); 8.11 (2H, br); 8.41 (1H, s); 8.73 (1H, d, J = 4.70 Hz). δ ^{13}C NMR (DMSO-d_6): 55.0; 104.7; 113.6; 113.8; 124.2; 127.9; 129.6; 138.9; 147.0; 154.1; 157.3; 159.0; 189.8. MS: M^+ = 252. HRMS: calcd for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0902.

5-Amino-6-(4-methoxyphenyl)-1-pyrindine-7-one (23). From 1.11 g of ethyl picolinate (7.34 mmol), 1.08 g of 4-methoxyphenylacetonitrile (7.37 mmol), and 22.2 mL of LDA (44.4 mmol) was obtained 1.83 g of the cyclic product (99%). Mp: 258.5−260 °C. δ ^{1}H NMR (DMSO-d_6): 3.78 (3H, s); 7.00 (2H, d, J = 8.23 Hz); 7.35 (1H, t, J = 12.4 Hz); 7.44 (2H, d, J = 8.22 Hz); 7.99 (1H, d, J = 7.30 Hz); 8.24 (2H, br); 8.44 (1H, d, J = 4.97 Hz). δ ^{13}C NMR (DMSO-d_6): 55.1; 104.2; 113.8; 124.4; 125.1; 133.6; 149.6; 154.8; 157.2; 159.6; 188.9. MS: M^+ = 252. HRMS: calcd for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0905.

Two-Step Reaction. (a) Keto Nitriles. The requisite amount of the nitrile was dissolved in THF, and 2 equiv of NaH was added to the solution, followed by 1 equiv of the aromatic ester. The mixture was then brought to reflux. After the reaction was complete as judged by TLC, it was cooled and brought to ice temperature. Water was added, and the bulk of THF was removed under reduced pressure. The aqueous layer was washed with dichloromethane and then acidified with 1 M HCl to give a precipitate. This was extracted with dichloromethane, and the extracts were washed with saturated sodium bicarbonate and then with water. The organic layer was dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give an oil. The latter (keto-nitrile) was either used as such for the next step or triturated with hexane/ethyl acetate to yield the solid product. **(b) Cyclization of Keto Nitriles.** The requisite amount of keto nitrile was added to 4 equiv of LDA at −10 °C. The reaction was left to stir overnight. After it was complete, it was worked up the same way as per the one-stage reaction.

3-Amino-2-(4-methoxyphenyl)-5-methoxy-1-indenone (Table 1, Entry 1). From 6.14 g of methyl 4-methoxybenzoate (36.9 mmol), 5.42 g of 4-methoxyphenylacetonitrile (36.8 mmol), and 2.98 g of NaH (74.5 mmol), 7.60 g of the keto nitrile[11] was obtained (74%). Second step: From 7.60 g of the keto nitrile (27.0 mmol) and 61.0 mL of LDA (122.0 mmol) was obtained 6.10 g of the 3-aminoindenone (80%). Overall yield: 59%.

3-Amino-2-(4-methoxyphenyl)-1-indenone (Table 1, Entry 2). From 1.06 g of methyl benzoate (7.78 mmol), 1.11 g of 4-methoxyphenylacetonitrile (7.54 mmol), and 0.790 g of NaH (19.8 mmol) there was obtained 1.35 g of the keto nitrile[11] (64%). Second step: From 0.700 g of the keto nitrile (2.79 mmol) and 6.00 mL of LDA (12.0 mmol) was obtained 0.610 g of the 3-aminoindenone (87%). Overall yield: 55.5%.

3-Amino-2-(2-methoxyphenyl)-5-methoxy-1-indenone (Table 1, Entry 3). From 5.64 g of methyl 4-methoxybenzoate (33.9 mmol), 5.00 g of 2-methoxyphenylacetonitrile (34.0 mmol), and 2.76 g of NaH (69.0 mmol) there was obtained 8.10 g of the keto nitrile[12] (85%). Second step: From 7.64 g of the keto nitrile (27.2 mmol) and 54.4 mL of LDA (108.8 mmol) was obtained 6.08 g of the 3-amino-indenone (80%). Overall yield: 69%.

3-Amino-2-(2-methoxyphenyl)-1-indenone (Table 1, Entry 4). From 5.40 g of methyl benzoate (39.7 mmol), 5.88 g of 2-methoxyphenylacetonitrile (38.7 mmol), and 3.22 g of NaH

(11) Cook, C. E.; Corley, R. C.; Wall, M. E. *J. Org. Chem.* **1965**, *30*, 4114.

(12) Chatterjea, J. N. *J. Ind. Chem. Soc.* **1970**, *47*, 4261.

(80.5 mmol) there was obtained 6.63 g of the keto nitrile[13] (68%). Second step: From 6.63 g of the keto nitrile (26.4 mmol) and 63.0 mL of LDA (126.0 mmol) was obtained 4.20 g of the 3-aminoindenone (64%). Overall yield: 43%.

3-Amino-2-(4-methoxyphenyl)-4-chloro-1-indenone (Table 1, Entry 6). From 5.00 g of methyl 3-chlorobenzoate (29.3 mmol), 4.31 g of 4-methoxyphenylacetonitrile (29.3 mmol), and 2.34 g of NaH (58.5 mmol) there was obtained 5.31 g of the keto nitrile (64%). δ ^{1}H NMR ($CDCl_3$): 3.79 (3H, s); 5.48 (1H, s); 6.91 (2H, d, J = 8.65 Hz); 7.30−7.42 (3H, m); 7.55 (1H, d, J = 8.21 Hz); 7.78 (1H, d, J = 7.79 Hz); 7.90 (1H, s). δ ^{13}C NMR ($CDCl_3$): 46.2; 55.4; 115.2; 116.6; 121.9; 127.2; 129.2; 129.5; 130.3; 134.2; 134.9; 135.3; 159.8; 188.3. MS: M^+=285. HRMS: calcd for $C_{16}H_{12}NO_2{}^{35}Cl$ 285.0561, found 285.0559. Second step: From 5.04 g of the keto nitrile (18.6 mmol) and 37.3 mL of LDA (74.4 mmol) was obtained 4.37 g of the 3-aminoindenone (75%). Overall yield: 56%.

3-Amino-2-phenyl-5-methoxy-1-indenone (Table 1, Entry 7). From 1.40 g of methyl 4-methoxybenzoate (8.40 mmol), 0.970 g of phenylacetonitrile (8.28 mmol), and 0.660 g of NaH (16.5 mmol) there was obtained 1.54 g of the keto-nitrile[14] (74%). Second step: From 0.110 g of the keto nitrile (0.480 mmol) and 0.900 mL of LDA (1.80 mmol) was obtained 0.0830 g of the 3-aminoindenone (75%). Overall yield: 56%.

3-Amino-2-phenyl-1-indenone (Table 1, Entry 8). From 2.49 g of ethyl benzoate (16.6 mmol), 1.95 g of phenylacetonitrile (16.6 mmol), and 1.34 g of NaH (16.5 mmol) there was obtained 2.72 g of the keto-nitrile[15] (75%). Second step: From 0.700 g of the keto nitrile (3.17 mmol) and 7.30 mL of LDA (14.6 mmol) was obtained 0.45 g of the 3-aminoindenone (64%). Overall yield: 48%.

3-Amino-2-(4-methoxyphenyl)-7-methoxy-1-indenone (Table 1, Entry 9). From 3.67 g of methyl 2-methoxybenzoate (22.1 mmol), 3.26 g of 4-methoxyphenylacetonitrile (22.2 mmol), and 1.78 g of NaH (44.5 mmol) there was obtained 4.41 g of the keto nitrile[16] (71%). Second step: From 4.22 g of the keto-nitrile (15.0 mmol) and 30.0 mL of LDA (60.0 mmol) was obtained 2.71 g of the 3-aminoindenone (64%). Overall yield: 45.5%.

3-Amino-2-(3-methoxyphenyl)-1-indenone (Table 1, Entry 11). From 1.08 g of ethyl benzoate (7.19 mmol), 1.05 g of 3-methoxyphenylacetonitrile (7.16 mmol), and 0.590 g of NaH (14.8 mmol) was obtained 1.28 g of the keto nitrile[17] (71%). Second step: From 1.21 g of the keto nitrile (4.82 mmol) and 9.64 mL of LDA (19.3 mmol) there was obtained 0.870 g of the 3-aminoindenone (72%). Overall yield: 51%. Mp: 234.5−235.5 °C. δ ^{1}H NMR (DMSO-d_6): 3.78 (3H, s); 6.75 (1H, d, J = 7.96 Hz); 7.08 (2H, s); 7.26−7.47 (4H, m); 7.72 (1H, d, J = 6.67 Hz); 8.08 (2H, br). δ ^{13}C NMR (DMSO-d_6): 54.8; 103.0; 110.6; 113.4; 118.9; 119.4; 120.4; 129.1; 130.4; 131.1; 134.2; 135.0; 138.1; 159.1; 161.8; 189.7. MS: M^+ = 251. HRMS: calcd for $C_{16}H_{13}NO_2$ 251.0946, found 251.0954.

5-Amino-6-(4-methoxyphenyl)-2-pyrindin-7-one (16). From 4.46 g of ethyl nicotinate (29.5 mmol), 4.34 g of 4-methoxyphenylacetonitrile (29.5 mmol), and 2.36 g of NaH (59.0 mmol) there was obtained 5.25 g of the keto nitrile[11] (78%). It is worth mentioning here that a minimum amount of acetic acid was used in the workup, as opposed to 1 M HCl with the other keto nitriles. That is necessary to avoid forming the pyridinium salt. Second step: From 2.05 g of the keto nitrile (8.13 mmol) and 16.3 mL of LDA (32.6 mmol) there was obtained 1.68 g of the cyclic product (82%). Overall yield: 64%.

7-Amino-6-(4-methoxyphenyl)-2-pyrindin-5-one (21). From 1.01 g of ethyl isonicotinate (6.68 mmol), 0.980 g of 4-methoxyphenylacetonitrile (6.68 mmol), and 0.560 g of NaH (14.0 mmol) there was obtained 1.09 g of the keto nitrile **20** (66%). δ ^{1}H NMR (DMSO-d_6): 3.76 (3H, s); 7.01 (3H, d, J = 8.80 Hz); 7.64−7.73 (3H, m); 8.76 (2H, d, J = 5.53 Hz). δ ^{13}C NMR (DMSO-d_6): 55.2; 89.9; 114.0; 114.3; 120.7; 123.2; 123.6; 124.9; 129.0; 129.5; 130.9; 143.6; 150.0; 158.4; 164.2. MS: M^+ = 252. HRMS: calcd for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0905. Second step: this was unsuccessful at first because the keto nitrile **20** is highly insoluble in THF. It was decided then to heterogeneously add the keto nitrile onto LDA. From 0.260 g of the keto nitrile (1.03 mmol) and 2.00 mL of LDA (4.0 mmol) there was obtained 0.180 g of the cyclic product **21** (69%). Overall yield: 46%. Mp: 281−282 °C. δ ^{1}H NMR (DMSO-d_6): 3.77 (3H, s); 6.98 (2H, d, J = 8.63 Hz); 7.29 (1H, d, J = 4,26 Hz); 7.42 (2H, d, J = 8.74 Hz); 8.34 (2H, br); 8.69 (1H, d, J = 4.36 Hz); 8.83 (1H, s). δ ^{13}C NMR (DMSO-d_6): 55.1; 103.8; 113.8; 124.9; 129.5; 132.2; 138.4; 143.4; 153.6; 157.5; 161.5; 188.2. MS: M^+ = 252. HRMS: calcd for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0904.

3-Amino-2-(3-pyridyl)-1-indenone (Table 2, Entry 5). From 1.22 g of 3-pyridylacetonitrile (10.3 mmol), 1.40 g of methyl benzoate (10.3 mmol), and 0.880 g of NaH (21.9 mmol) there was obtained 1.63 g of the keto nitrile[18] (63%). Second step: From 0.520 g of the keto nitrile (2.36 mmol) and 5.00 mL of LDA (10.0 mmol) there was obtained 0.230 g of the 3-aminoindenone (44%). Overall yield: 28%. Note: the second step was done neat. Mp: 279.5−280 °C. δ ^{1}H NMR (DMSO-d_6 + 1 drop of D_2O): 7.36−7.50 (4H, m); 7.73 (1H, d, J = 7.30 Hz); 7.85 (1H, d, J = 4.91 Hz); 8.34 (1H, d, J = 4.70 Hz); 8.67 (1H, s). δ ^{13}C NMR (DMSO-d_6): 99.9; 119.9; 119.7; 123.3; 129.1; 130.7; 131.3; 134.9; 138.0; 145.5; 148.8; 162.4; 189.6. MS: M^+=222; HRMS: calcd for $C_{14}H_{10}N_2O$ 222.0793, found 222.0792. An X-ray analysis was performed on this compound.[4]

3-Amino-2-(4-methoxyphenyl)-1-[benz][*e*]-1-indenone (12). From 1.37 g of 1-methylnaphthoate (7.36 mmol), 1.08 g of 4-methoxyphenylacetonitrile (7.35 mmol), and 0.600 g of NaH (15.1 mmol) was obtained 1.28 g of the keto nitrile **11** (58%). This compound was recrystallized from toluene. δ ^{1}H NMR ($CDCl_3$); 3.86 (3H, s); 7.02 (2H, d, J = 8.78 Hz); 7.61−7.76 (5H, m); 7.91 (1H, m); 8.10 (2H, d, J = 8.43 Hz); 12.1 (1H, s). δ ^{13}C NMR (DMSO-d_6): 55.2; 90.4; 113.9; 114.1; 120.5; 124.9; 125.1; 125.5; 125.6; 126.7; 127.4; 127.5; 128.4; 128.6; 128.9; 129.1; 129.5; 130.3; 130.5; 133.4; 134.0; 158.3; 165.0. MS: M^+ = 301. HRMS: calcd for $C_{20}H_{15}NO_2$ 301.1103, found 301.1107. Second step: From 0.710 g of the keto-nitrile (2.36 mmol) and 4.65 mL of LDA (9.30 mmol) was obtained 0.500 g of the cyclic product **12** (70%). Overall yield: 41%.

3-Amino-2-cyano-1-indenone (Table 2, Entry 4). To a mixture of 6.60 g of malononitrile (100 mmol) and 16.6 g of anhydrous potassium carbonate (120 mmol) was added gradually 36.2 g of benzoic anhydride (160 mmol). The mixture was stirred at room temperature, cooled, dissolved in water, acidified with HCl, and extracted with diethyl ether. The ether extracts were washed with brine solution, dried with sodium sulfate, filtered, and concentrated under reduced pressure to reveal 20.4 g of a yellow solid that was found to be 2-cyano-3-oxo-3-phenyl propionitrile.[19] Yield: 75%. MS: M^+ = 170. Second step: From 3.96 g of the keto-nitrile (23.3 mmol) and 47.0 mL of LDA (94.0 mmol) there was obtained 0.700 g of the 3-aminoindenone (18%). Overall yield: 13.5%. Mp: >275 °C. δ ^{1}H NMR (DMSO-d_6): 7.44 (1H, t, J = 5.10 Hz); 7.58−7.62 (2H, m); 7.87 (1H, dd, J = 6.60 Hz, J = 1.20 Hz); 9.63 (2H, br). δ ^{13}C NMR (DMSO-d_6): 75.3; 115.4; 120.9; 121.2; 132.3; 132.8; 134.8; 135.4; 169.7; 187.7. MS: M^+ = 170; HRMS: calcd for $C_{10}H_6N_2O$ 170.0480, found 170.0490.

2-Bromobenzoylacetonitrile (35). From 8.78 g of ethyl 2-bromobenzoate (38.3 mmol), 1.57 g of acetonitrile (38.3 mmol), and 3.13 g of NaH (78.2 mmol) was obtained 6.49 g of the keto nitrile (**35**) (76%). The compound was purified by column chromatography (3/1 hexanes−ethyl acetate).

2-Deuteriobenzoylacetonitrile (37). Dissolving **35** in deuterated $CDCl_3$, followed by D_2O and a trace amount of tetrabutylamonium bromide, revealed the dideutero labeled compound **36** after about 1 h. A 0.420 g portion of **36** was dissolved in 10 mL of THF. The solution was brought to −78

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°C, and 2.44 mL of *t*-BuLi (4.15 mmol) was added. The reaction mixture turned dark, and an exotherm occurred. It was left to stir until it reached room temperature. It was quenched with 5 mL of water. The bulk of THF was removed under reduced pressure. The aqueous layer was then washed with dichloromethane and then acidified with 1 M HCl, which was then extracted with dichloromethane. The organic phase was dried with magnesium sulfate, filtered, and concentrated under reduced pressure to reveal a brown solid. This was recrystallized from an ether−hexane solvent pair to give **37** as a white solid.

Hydrolysis of 3-Aminoindenones to 1,3-Indandiones: General Procedure. The 3-aminoindenone was added to 20% sulfuric acid in water. The heterogeneous mixture was refluxed. After about half an hour, the dark red color disappeared and a white solid could be seen. That solid was extracted three times with dichloromethane which was then washed with deionized water followed by brine solution. It was then dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was typically recrystallized from anhydrous ethanol to yield a white compound.

2-(4-Methoxyphenyl)-5-methoxy-1,3-indandione (Table 1, Entry 1). From 2.02 g of 3-amino-2-(4-methoxyphenyl)-5-methoxyindenone (7.19 mmol) and 50 mL of sulfuric acid there was obtained 1.20 g of the 1,3-indandione (61%). Mp: 167−168 °C. δ ^{1}H NMR ($CDCl_3$): 3.83 (3H, s); 3.98 (3H, s); 4.20 (1H, s); 6.88 (2H, d, J = 8.40 Hz); 7.10 (2H, d, J = 8.70 Hz); 7.41 (2H, s); 7.96 (1H, d, J = 1.50 Hz). δ ^{13}C NMR ($CDCl_3$): 55.3; 56.3; 59.4; 104.9; 114.5; 124.9; 125.4; 129.8; 135.9; 145.2; 159.8; 165.2; 197.4; 199.6. MS: M^+=282; HRMS: calcd for $C_{17}H_{14}O_4$ 282.0892, found 282.0887.

2-(4-Methoxyphenyl)-1,3-indandione (Table 1, Entry 2). From 0.129 g of 3-amino-2-(4-methoxyphenyl)-1-indenone (0.514 mmol) and 5 mL of sulfuric acid there was obtained 0.102 g of the 1,3-indandione (79%). Mp: 153.5−154.5 °C. δ ^{1}H NMR ($CDCl_3$): 3.77 (3H, s); 4.21 (1H, s); 6.86 (2H, d, J = 9.14 Hz); 7.10 (2H, d, J = 8.70 Hz); 7.88 (2H, dd, J = 12.4 Hz; J = 3.00 Hz); 8.04 (2H, dd, J = 12.6 Hz; J = 5.64 Hz). δ ^{13}C NMR ($CDCl_3$): 55.3; 59.1; 114.5; 123.7; 125.2; 129.9; 136.0; 142.6; 159.8; 198.7. MS: M^+ = 252. HRMS: calcd for $C_{16}H_{12}O_3$ 252.0786, found 252.0794.

2-(2-Methoxyphenyl)-5-methoxy-1,3-indandione (Table 1, Entry 3). From 0.241 g of 3-amino-2-(2-methoxyphenyl)-5-methoxy-1-indenone (0.858 mmol) and 21 mL of sulfuric acid there was obtained 0.196 g of the 1,3-indandione (81%). Mp: 173−174 °C. δ ^{1}H NMR ($CDCl_3$): 3.76 (3H, s); 3.96 (3H, s); 4.18 (1H, s); 6.78 (1H, d, J = 8.18 Hz); 6.98 (1H, t, J = 14.8 Hz); 7.21−7.38 (4H, m); 7.93 (1H, d, J = 8.28 Hz). δ ^{13}C NMR ($CDCl_3$): 55.4; 56.1; 59.9; 104.6; 111.0; 121.2; 122.5; 124.0; 124.9; 129.6; 132.6; 135.0; 144.1; 157.7; 165.2; 197.5; 199.8. MS: M^+ = 282; HRMS: calcd for $C_{17}H_{14}O_4$ 282.0892, found 282.0896.

2-(4-Methoxyphenyl)-4-chloro-1,3-indandione (Table 1, Entry 6). From 0.375 g of 3-amino-2-(4-methoxyphenyl)-4-chloro-1-indenone (1.31 mmol) and 15 mL of sulfuric acid there was obtained 0.224 g of the 1,3-indandione (60%). Mp: 137.5−139.5 °C. δ ^{1}H NMR ($CDCl_3$): 3.78 (3H, s); 4.23 (1H, s); 6.87 (2H, d, J = 8.61 Hz); 7.10 (2H, d, J = 8.63 Hz); 7.75−7.83 (2H, m); 7.96 (1H, dd, J = 8.27 Hz; J = 4.38 Hz). δ ^{13}C NMR ($CDCl_3$): 55.3; 59.2; 114.5; 122.1; 124.7; 129.9; 132.3; 136.4; 137.6; 144.3; 159.3; 195.7; 198.2. MS: M^+ = 286 and 288. HRMS: calcd for $C_{16}H_{11}O_3Cl$ 286.0397, found 286.0402.

2-Phenyl-5-methoxy-1,3-indandione (Table 1, Entry 7). From 0.155 g of 3-amino-2-phenyl 1-indenone (0.618 mmol) and 10 mL of sulfuric acid was obtained 0.114 g of the 1,3-indandione (74%). Mp: 184−185 °C. δ ^{1}H NMR ($CDCl_3$): 3.97 (3H, s); 4.24 (1H, s); 7.17 (2H, d, J = 6.02 Hz); 7.19−7.41 (5H, m); 7.97 (1H, d, J = 9.02 Hz). δ ^{13}C NMR ($CDCl_3$): 56.2; 60.1; 104.9; 124.9; 125.5; 127.8; 128.7; 129.0; 133.5; 136.1; 166.2; 170.1; 196.2; 198.7. MS: M^+ = 252; HRMS: calcd for $C_{16}H_{12}O_3$ 252.0786, found 252.0789.

2-(4-Methoxyphenyl)-4,5,6-trimethoxy-1,3-indandione (Table 1, Entry 13). From 0.240 g of 3-amino-2-(4-methoxyphenyl)-4,5,6-trimethoxy-1-indenone (0.700 mmol) and 15 mL of 20% sulfuric acid there was obtained 0.200 g of the pink 1,3-indandione (83%). Both ^{1}H and ^{13}C NMR spectra suggest a large amount of the enol tautomer present. Mp: 132−133 °C. δ ^{1}H NMR ($CDCl_3$): 3.76−3.81 (3H, s); 3.87−3.91 (3H, s); 4.00−4.01 (3H, s); 4.05−4.10 (3H, s); 4.13 (1H, s); 6.86 (2H, d, J = 8.62 Hz); 6.96 (1H, d, J = 11.8 Hz); 7.09 (1H, d, J = 8.58 Hz); 7.37−7.40 (1H, d, J = 9.25 Hz). δ ^{13}C NMR ($CDCl_3$): 55.14; 56.43; 56.68; 59.22; 60.89; 61.27; 61.47; 62.29; 100.65; 102.64; 114.36; 114.40; 124.74; 125.73; 128.57; 128.99; 129.75; 139.52; 148.46; 151.07; 159.20; 160.36; 195.03; 198.14.

3-Amino-2-(4-methoxyphenyl)-1,3-[benz][*e*]indandione (13). From 0.230 g of 3-amino-2-(4-methoxyphenyl)-1-[benz][*e*]indenone (0.764 mmol) and 10 mL of 20% sulfuric acid there was obtained 0.190 g of the product (83%). Mp: 177−179 °C. δ ^{1}H NMR ($CDCl_3$): 3.79 (3H, s); 6.89 (2H, dd, J = 9.00 Hz, J = 4.5 Hz); 7.16 (2H, dd, J = 9.00 Hz, J = 4.20 Hz); 7.81 (2H, q, J = 17.4 Hz); 8.02 (2H, t, J = 8.40 Hz); 8.30 (1H, d, J = 8.70 Hz). 9.27 (1H, d, J = 9.90 Hz). δ ^{13}C NMR ($CDCl_3$): 55.61; 59.43; 114.94; 118.96; 126.05; 127.30; 128.61; 129.14; 130.31; 130.50; 130.72; 137.62; 137.85; 139.40; 143.73; 159.73; 199.46; 200.38. MS: M^+ = 302. HRMS: calcd for $C_{20}H_{14}O_3$ 302.0943, found 302.0941.

6-(4-Methoxyphenyl)-2-pyrindine-5,7-dione (17). In a 25 mL rounded-bottomed flask was added 0.200 g of 5-amino-6-(4-methoxyphenyl)-2-pyrindin-7-one (0.790 mmol) to 5 mL water, followed by 5 mL 48% HBr. The mixture was refluxed for 5 h and then cooled to room temperature. The solution was made basic with 1 M NaOH and reacidified by using acetic acid. The purple solid that precipitated was washed with water. Yield: 0.170 g or 85%. Mp: 243−244 °C. δ ^{1}H NMR (DMSO-d_6): 3.78 (3H, s); 6.82 (2H, d, J = 7.50 Hz); 7.58 (1H, d, J = 5.02 Hz); 8.38 (3H, t, J = 15.0 Hz); 8.78 (1H, d, J = 6.40 Hz). δ ^{13}C NMR ($CDCl_3$): 54.85; 110.31; 113.04; 113.47; 114.50; 126.32; 126.72; 127.97; 128.10; 134.98; 147.71; 155.89; 156.08; 181.01; 185.55. MS: M^+ = 253. HRMS: calcd for $C_{15}H_{11}NO_3$ 252.0739, found 253.0742.

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Supporting Information Available: Complete ^{1}H and ^{13}C nuclear magnetic resonance spectra are available for all of the aminoindenones and the indandiones reported in this paper except the ^{13}C NMR data for compounds **12**, **17**, and the indandiones reported in Table 1 as entries 1 and 13 (all these compounds had poor solubility in DMSO). This material is available free of charge via the Internet at http://www.acs.org.

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