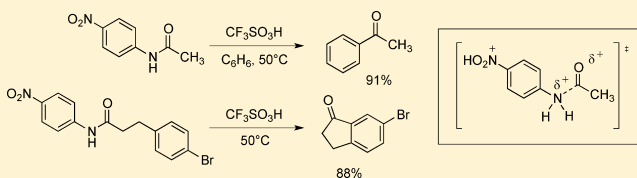# Friedel−Crafts Acylation with Amides

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Ⓢ Supporting Information

ABSTRACT: Friedel−Crafts acylation has been known since the 1870s, and it is an important organic synthetic reaction leading to aromatic ketone products. Friedel−Crafts acylation is usually performed with carboxylic acid chlorides or anhydrides, while amides are generally not useful substrates in these reactions. Despite being the least reactive carboxylic acid derivative, we have found a series of amides capable of providing aromatic ketones in good yields (55−96%, 17 examples). We propose a mechanism involving diminished C−N resonance through superelectrophilic activation and subsequent cleavage to acyl cations.

INTRODUCTION

In 1877, Friedel and Crafts reported the synthesis of an aryl ketone with the use of a carboxylic acid chloride, aluminum chloride, and benzene.[1] The Friedel−Crafts acylation may now be accomplished with carboxylic acids as well as carboxylic acid derivatives, esters, and anhydrides.[2] A wide variety of Lewis and Brønsted acids are also known to promote these electrophilic aromatic substitutions.[3] The Friedel−Crafts acylation is a vitally important conversion for industry, as it is used to prepare chemical feedstock, synthetic intermediates, and fine chemicals.[4]

Despite the long history of Friedel−Crafts acylation, there has been almost nothing reported in which amides are used in these conversions. Most Friedel−Crafts acylations are thought to occur via reactive acyl cation intermediates.[5] However, the strong carbon−nitrogen bond in amides inhibits cleavage to acyl cations under acidic conditions. This has effectively prevented amides from being used in Friedel−Crafts acylation. Though amides are generally not considered viable substrates for the Friedel−Crafts synthesis of aromatic ketones, recent studies have shown that destabilized amides can give these products in good yields. For example, β-lactams were shown to give aryl ketones from Friedel−Crafts reactions.[6] These reactions are clearly driven by the release of strain in the β-lactam ring system. We recently described several examples of Friedel−Crafts acylation using heterocyclic and amino amides (eq 1).[7] The chemistry utilized a Brønsted superacid
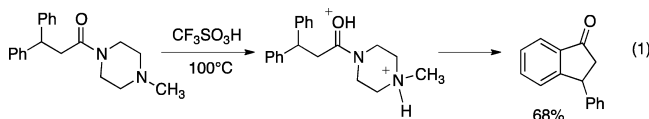
(CF$_3$SO$_3$H), and a mechanism was proposed with dicationic superelectrophiles in the transformations. Presumably, these conversions are driven by the repulsive interaction of cationic charge centers in the dicationic intermediates. Regarding amide

activation, recent reports have also shown that decreasing amide resonance interactions can influence the reactivity of this functional group. For example, dramatically increased amide hydrolysis rates (nucleophilic attack by water) have been induced by decoupled resonance of the amide through torsional strain.[8] Solvolysis of amides and ureas have also been shown to occur readily by decoupled resonance involving protonation at the amido nitrogen.[9]

These previous studies suggested that a general synthetic route might be possible for the use of amides in Friedel−Crafts chemistry, especially if the amide resonance could be diminished. In this report, we describe a synthetic methodology for the use of amides to prepare aryl ketones. The chemistry is shown to be effective in intramolecular and intermolecular reactions. In some cases, the acylation is comparable to or better than similar reactions with carboxylic acid chlorides. Moreover, the chemistry is done with a recyclable Brønsted acid and recoverable amine component. A mechanism is proposed that involves decreasing amide resonance and cleavage to acyl cations.

RESULTS AND DISCUSSION

Initial experimentation focused on the development of intramolecular acylation leading to indanones and related products. A series of 3-phenylpropanamides (**1a−d**) were prepared and reacted with the Brønsted superacid CF$_3$SO$_3$H (triflic acid) to form 1-indanone (**2**) by cyclization (Figure 1).

By varying the N-substituent, the 3-phenylpropanamides were designed to reduce the resonance interaction between the nitrogen and carbonyl groups through inductive or resonance-type interactions. For example, perfluorinated aryl groups are known to exert powerful electron-withdrawing properties.[10] As such, this should weaken the amide resonance and lead to acyl
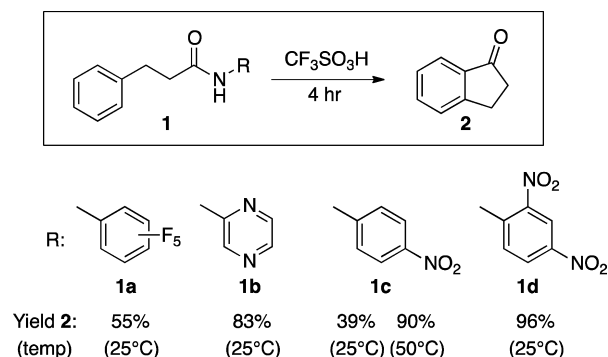
Figure 1. Isolated yields for cyclizations of amide derivatives **1a–d**.

transfer. When amide **1a** is reacted with triflic acid in CHCl$_3$ (25 °C), a fair yield of 1-indanone (**2**) is obtained. Recent studies have also shown that protonated pyrazinyl- and nitro-substituted aryl groups can exert strong electron-withdrawing effects.[11,12] Thus, amides **1b–d** lead to 1-indanone in good yields. The dinitrophenyl group showed the highest degree of activation, as it provided compound **2** in 96% yield. In the case of **1c**, a significant increase in yield was observed by raising the reaction temperature from 25 to 50 °C (39% → 90%). In the optimized procedure, the byproduct 4-nitroaniline may be recovered in at least 90% yield. Amide **1c** was also reacted with other acids (H$_2$SO$_4$, CF$_3$CO$_2$H, AlCl$_3$, HY-zeolite, Sc(OTf)$_3$), but only CF$_3$SO$_3$H successfully converted **1c** to the indanone **2**.

Utilizing the 4-nitroaniline as the activating group, a series of functionalized indanones were prepared from the amides (Table 1). Alkyl-substituted 1-indanones (**8–9**) were formed in good yield, although under the reaction conditions some isomerization of **8** occurs (isopropyl group migrates on ring) and the isolated yield is reduced. The methoxy- and bromo-substituted products (**10–11**) are also obtained in good yield.

Table 1. Intramolecular Reactions of Amides 3–7 To Give 8–12

^{a}Isolated yields. ^{b}Reaction with 4 equiv of CF$_3$SO$_3$H, CHCl$_3$, 50 °C, 4 h. ^{c}Reaction with 4 equiv of CF$_3$SO$_3$H, C$_6$H$_6$, 50 °C, 4 h.

Unsaturated amides are known to undergo addition reactions with arenes via superelectrophilic intermediates.[7,13] Consequently, arylation may be coupled with cyclization to give the phenyl-substituted 1-indanone (**12**). Using this strategy, amide **7** may be reacted with o-dichlorobenzene in superacid to provide direct access to indanone **13** (eq 2), an intermediate
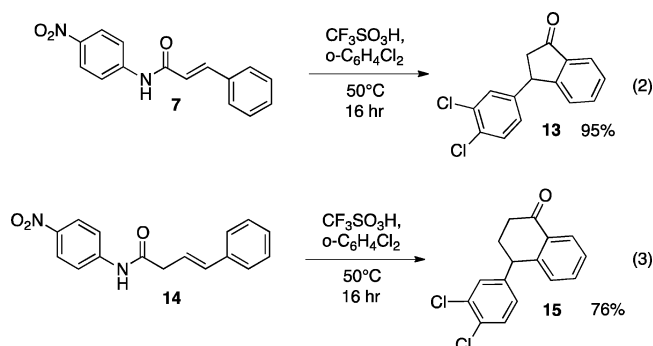

used in the synthesis of the monoamine transport inhibitor indatraline. The tetralone product (**15**) may similarly be prepared from amide **14** (eq 3). Compound **15** is a synthetic intermediate used to prepare the antidepressant drug sertraline. Assuming that arylation is the initial step, products **13** and **15** are then formed by cyclization into the more highly electron-rich aryl group.

We have also found this chemistry to be effective in the synthesis of aromatic ketones by intermolecular reactions, for example, the reactions of N-(4-nitrophenyl)acetamide (**16**) and N-(4-nitrophenyl)benzamide (**17**) with benzene in CF$_3$SO$_3$H (Scheme 1). The reactions were conducted with 4.0 equiv of CF$_3$SO$_3$H at 50 °C (3 h reaction). Both amide substrates provide the desired aromatic ketones in excellent yields. For example, compound **17** gives benzophenone (**19**) in 93% yield (eq 4). The byproduct, p-nitroaniline, may be recovered in greater than 80% yield, and triflic acid may itself be quantitatively recycled.[14] A recent study also showed that amide **17** may be prepared directly in 95% yield from benzoic acid and p-nitroaniline by simple dehydration over sulfated nanoscale titania.[15] Since both triflic acid and p-nitroaniline can be reused, *this Friedel–Crafts acylation represents a conversion producing minimal chemical waste*. The benzamide derivative **17** likewise gives good yields of the aromatic ketones **20–22** from the respective arenes. These yields are comparable to synthetic reactions that use carboxylic acid chlorides or anhydrides leading to benzophenone (**19**) and related ketones. For example, benzophenone (**19**) has been prepared recently by a variety of methods using benzoyl chloride and the product yields vary from 50 to 97%.[16] At 93% yield of benzophenone, our amide-based methodology is competitive with the highest yielding methods with benzoyl chloride. Interestingly, benzophenone (**19**) is also prepared in good yield from direct reaction of the p-nitrophenylisocyanate (**23**) from CF$_3$SO$_3$H and benzene (Scheme 1, eq 5). Isocyanates are known to form aromatic amides by electrophilic aromatic substitution.[17] Thus, the isocyanate **23** leads to amide **17** and this reacts further to give benzophenone (**19**). In this conversion, compound **23** functions as a novel phosgene equivalent, as it provides only the carbonyl group in the final product.

With respect to reaction mechanisms, Friedel–Crafts acylation with carboxylic acid chlorides or anhydrides often occurs through acyl cation intermediates;[5] however, amides

Scheme 1. Products and Yields from Intramolecular Reactions
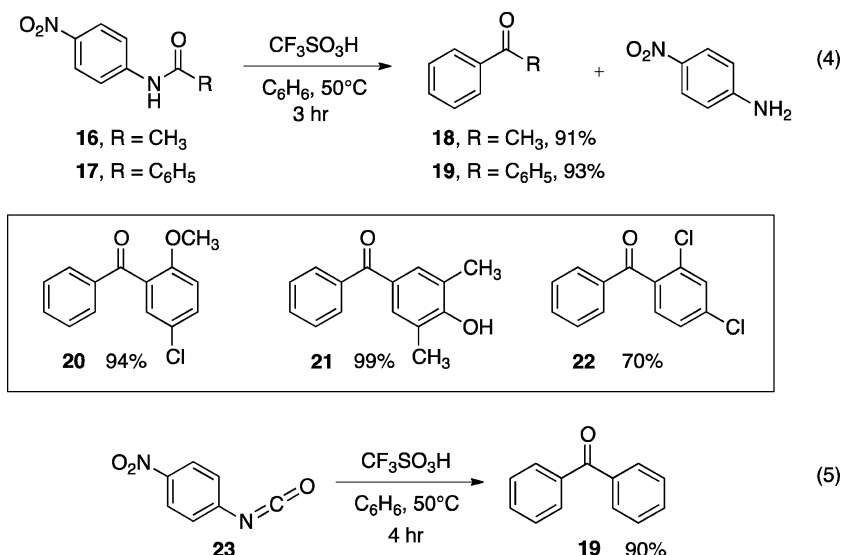
generally do not produce acyl cations in acidic media. Nevertheless, amide **17** reacts with CF_3SO_3H (4 equiv) in CH_2Cl_2 (no arene nucleophile), and when the mixture is poured over ice, benzoic acid is isolated in 90% yield and no starting amide is found. This observation is consistent with the formation of either the benzoyl cation or the mixed anhydride with the triflate anion.

Attempts to directly observe an acyl cation by NMR spectroscopy were not successful; however, increasing the electron-withdrawing properties of the amide substituent does lead to strongly deshielded amide carbonyl groups (Table 2). Three amides were studied for comparison purposes: acetanilide (**24**), 4-nitroacetanilide (**16**), and 2,4-dinitroacetanilide (**25**). These systems were analyzed by ^{13}C NMR spectroscopy from solutions of varying acidity—DMSO (nonacidic), CF_3CO_2H (H_o −2.7), and FSO_3H (H_o −15.1).[18] All spectra were obtained at 25 °C. Computational studies were also performed to compare calculated results with the experimental data.[16] NMR chemical shifts were calculated using B3LYP/IGLO-II as implemented in Gaussian 03 on gas-phase-optimized structures with tetramethylsilane as the NMR reference.[19] The amide carbonyl resonances are observed at about δ 169 in DMSO solution, while solvation in CF_3CO_2H leads to carbonyl resonance around δ 174. The downfield shift is likely due to partial protonation of the amide carbonyl group (amide carboxonium ion, pK_a ∼ −0.5) in CF_3CO_2H (pK_a 0.52).[20,21] Interestingly, the presence of the nitro group(s) has little cumulative effect on the carbonyl signal in CF_3CO_2H, as all three systems exhibit δ 174. This is likely the result of competing factors. The nitro substituents may decrease the basicity of the carbonyl group, and thus, compound **25** could be protonated to less of an extent at the carbonyl group than compound **24** so the carbonyl group of **25** could be shielded relative to **24**. But the nitro substituents are also interacting with the acidic solvent by hydrogen bonding, and this may cause a deshielding of the carbonyl carbon of **25**.

Fluorosulfonic acid was used in the NMR experiments because its acid strength (H_o −15.1) is comparable to triflic acid (H_o −14.1), the catalyst used in the synthetic reactions. Moreover, it has no ^{13}C NMR signals. The fluorosulfonic acid solutions exhibit two characteristic ^{13}C NMR spectra for amides

16, **24**, and **25**. Amide **24** shows a resonance at δ 175.2, which likely corresponds to the protonated species in the superacid media. Calculations located two isomeric carboxonium structures separated by just 0.9 kcal/mol. The lowest energy structure (**26**) exhibits resonance at δ 182.5, while the higher energy structure is at δ 174.0.[16] Thus, the experimentally observed signal may arise from an averaging of these two species. For amide **16**, a minor component of the equilibrium exhibits a carboxonium ion signal at δ 178.3 and a major component exhibits a highly deshielded carboxonium signal at δ 193.0. It is suggested that these two components of the mixture correspond to ions **27** and **29**. The deshielded carboxonium signal corresponds to the diprotonated species **29**, as the protonated nitro group competes with the protonated carbonyl group for the lone pair electrons on the amide nitrogen. This weakens the amide resonance (vida infra) and leads to deshielding of the carboxonium carbon. The calculated value for dication **29** is δ 190.6, which is reasonably close to the experimentally observed carboxonium ion signal. While protonation of the nitro group alone (**28**) does cause a downfield shift to the carbonyl group (relative to the starting amide **16**), the monoprotonated species **28** cannot account for the carboxonium signal at δ 193.0.[22] In the case of the dinitroacetanilide (**25**), solvation in superacid leads to a clean ^{13}C NMR spectrum, only a single set of peaks, having a downfield signal also at δ 193.0. The dinitrophenyl group leads to the strongly deshielded carboxonium ion, although it is not clear to what extent the nitro groups are protonated in the FSO_3H. Experimental and theoretical studies have previously shown the acetyl cation to exhibit ^{13}C NMR resonance at about δ 150.[23] None of the amides (**16**, **24**, **25**) showed ^{13}C NMR signals in this region of the spectrum under the experimental conditions (25 °C, ca. 30 min). In contrast, acetyl chloride reacts with fluorosulfonic acid to provide a single downfield peak at δ 151.1,[24] suggesting that the acetyl cation should be observable in the superacidic media (if formed in the NMR experiments).

In order to better understand the mechanism, a computational study was initiated to investigate both structural and reactivity effects upon treating the amides with superacids. In addition, activation barriers for the reactions were investigated

Table 2. Experimental and Calculated ^{13}C NMR Data for Amides 16, 24, and 25

24 in DMSO: 168.2, 139.3, 128.5, 122.9, 118.9, 23.9

24 in CF$_3$CO$_2$H: 174.9, 132.4, 128.5, 127.9, 122.3, 19.1

24 in FSO$_3$H: 175.2, 130.4, 129.2, 128.9, 122.3, 19.1

16 in DMSO: 169.8, 145.9, 142.2, 125.4, 119.0, 24.7

16 in CF$_3$CO$_2$H: 174.5, 143.5, 141.8, 124.2, 120.5, 20.9

16 in FSO$_3$H: (major) 193.0, 146.7, 133.7, 125.7, 124.3, 18.9
              (minor) 178.3, 144.6, 138.9, 125.9, 124.3, 19.8

25 in DMSO: 169.4, 142.8, 140.9, 137.3, 129.0, 125.3, 121.6, 24.2

25 in CF$_3$CO$_2$H: 174.2, 141.9, 137.5, 135.8, 129.2, 122.9, 121.0, 22.5

25 in FSO$_3$H: 193.0, 147.5, 140.6, 130.6, 128.1, 127.5, 122.1, 18.9

and alternative mechanistic pathways were considered. Full details of the computational methodology employed can be found in the Supporting Information. For *p*-nitroacetanilide (16), protonation equilibria led to monocations 27 and 28 (Figure 1). The nitro-protonated species 28 is found to be somewhat higher in energy (+6.7 kcal/mol), but it should be a trace component of the equilibrium mixture. We had observed that superacidic conditions are required for successful Friedel–Crafts acylation, suggesting the involvement of diprotonated intermediates. Moreover, NMR experiments with 16 suggested an equilibrium with dication 29 at 25 °C. The dication 29 is the most stable diprotonated species, having protonation at the nitro and amide oxygen atoms. Although amide bonds in general tend to prefer *O*-protonation, it has been observed that *N*-protonation may occur to a small extent in acidic media.[25] With *N*-protonation, dication 33 is formed which is calculated to be +15.9 kcal/mol less stable than 29. The activation barrier for C–N bond cleavage from the intermediate 33 is found to be only 2.3 kcal/mol, generating the acetyl cation 36 and eventually the *N*-protonated *p*-nitroaniline 37 in an exergonic series of reaction steps. Thus, the activation barrier for the C–N bond cleavage is found to be 18.2 kcal/mol above the most stable dication species (29). This is clearly a surmountable barrier at the reaction temperature (50 °C) used in the Friedel–Crafts reactions. Cleavage to the acetyl cation 36 and 35 is expected to be favorable as this eliminates charge–charge repulsive interactions in dication 33. With formation of the acetyl cation 36, reaction with benzene leads to acetophenone (2) via a classic Friedel–Crafts reaction pathway. Other plausible mechanisms were studied by calculations, including those with monocationic and tetrahedral intermediates, but strongly endergonic processes were required for these reaction pathways. Likewise, the dication species from double protonation of the amide group (at the amide nitrogen and oxygen sites) was also calculated and found to be more than 36 kcal/mol above 29, so this pathway is considered unlikely.

The calculated structures reveal a diminished amide resonance with ions 28 and 33. For *p*-nitroacetanilide (16), calculations show an amide C–N bond length of 1.39 Å, and with protonation of the nitro group (28) the bond lengthens to 1.43 Å. With lengthening of the amide C–N bond, rotation around the amide bond also becomes more favorable. The *p*-nitroacetanilide (16) itself exhibits a calculated amide rotational
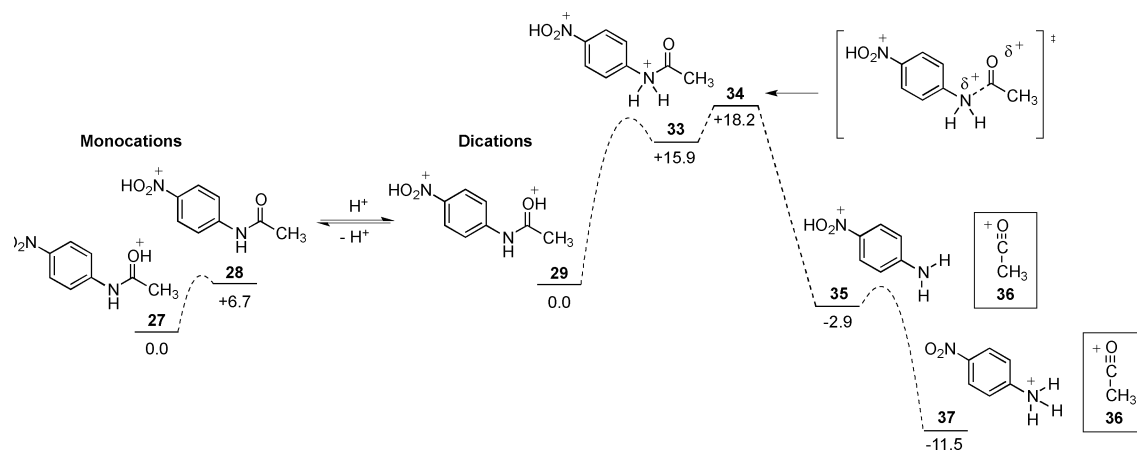
Figure 2. Calculated relative free energies (kcal/mol) in solution for M06/6-31G(d) optimized structures of intermediates and transition state (34) for amide 16 cleavage.

barrier of 14.5 kcal/mol, whereas protonation of the nitro group leads to an amide rotational barrier of 10.7 kcal/mol. Calculations indicate that dication **33** has an exceptionally long C−N bond (1.85 Å), as *N*-protonation completely eliminates resonance interactions. Likewise, the occupancy number of the amide π^*_{CO} progressively decreases from **16** (0.24 electrons) → **28** (0.17 electrons)→ **33** (0.08 electrons) while the amide n_N and $\sigma^*_{NC(O)}$ exhibit increasing occupancy within this series.[16] These data are consistent with a decreasing amount of amide resonance during the course of the reaction. Conversely, it is also found that carbonyl *O*-protonation leads to both a shortening of, and increased rotational barrier for the amide C−N bond, thus making the C−N bond less reactive. Other plausible mechanisms were studied by calculations, including those with monocationic and tetrahedral intermediates, but strongly endergonic processes were required for these reaction pathways.

As noted by Olah, an important aspect of superelectrophilic activation involves decreased neighboring group stabilization of an electrophilic center or functional group.[26] Earlier work by Shudo demonstrated the powerful electron withdrawing effects of the protonated nitro group in superelectrophilic intermediates.[12] A similar phenomenon occurs in our chemistry. Protonation of the nitro group leads to a decreasing amount of amide resonance, thus weakening the amide bond and opening up the new reaction pathway—cleavage to the acyl cation.

Although NMR experiments support the involvement of dicationic, superelectrophilic intermediates in the reactions, we were unable to observe the acetyl cation (**36**) by ^{13}C NMR analysis of the acetanilides in FSO$_3$H. This may be understood by consideration of the mild conditions used in the NMR experiments and the relatively high-energy barrier involved in cleavage to the acetyl cation (+18.2 kcal/mol). In the synthetic conversions, reaction conditions (50 °C over several hours) permit the reactive intermediate to be formed.

■ CONCLUSIONS

In summary, we have demonstrated a viable synthetic methodology for the use of amides in Friedel−Crafts acylation chemistry. The reactions have produced aromatic ketones in high yields from intra- and intermolecular reactions. Conventional Friedel−Crafts reactions, with acid chlorides or anhydrides, often require excess quantities of Lewis acid (i.e., AlCl$_3$), and they can produce significant amounts of corrosive vapor and aqueous aluminum waste. Our synthetic method is performed with an acid that may be recycled quantitatively, while the amine component may also be recovered and recycled. Thus, our chemistry minimizes the potential environmental impact of Friedel−Crafts acylation. We propose a mechanism involving superelectrophile formation, diminished amide resonance, and cleavage to the acyl cation.

■ EXPERIMENTAL SECTION

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. ^{1}H NMR and ^{13}C NMR were done using a 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, while high-resolution mass spectra were obtained from a commercial analytical laboratory (electron-impact ionization; sector instrument analyzer type).

Amide Synthesis, General Procedure A. The acid chloride (1 mmol) was added to a cooled (0 °C) solution of 4-nitroaniline (0.14 g, 1 mmol) in anhydrous THF (20 mL). The solution was stirred for 12 h at 25 °C, after which it was partitioned between cold water and ethyl ether. The organic layer was separated, washed with H$_2$O (2×) and brine (2×), and dried over anhydrous sodium sulfate. The crude product was isolated, and purification was done via column chromatography (100% ethyl ether).

Amide Synthesis, General Procedure B. The carboxylic acid (1 mmol), nitro-substituted aniline (1 mmol), EDCI (1.2 mmol), and DMAP (0.4 mmol) are dissolved in anhydrous dichloromethane (20 mL). The solution was stirred for 12 h at 25 °C, after which it was partitioned between cold water and CHCl$_3$. The organic layer was separated, washed with H$_2$O (2×) and brine (2×), and dried over anhydrous sodium sulfate. The crude product was isolated, and purification was done via column chromatography (hexane/ethyl acetate).

Indanone synthesis, General Procedure. Trifluoromethanesulfonic acid (0.35 mL, 4 mmol) was added to a solution of the amide substrate (1 mmol) in anhydrous CHCl$_3$ or CH$_2$Cl$_2$ (2 mL). The mixture was stirred for 4 h and then poured over ice. The products were extracted into CHCl$_3$, and the organic solution was washed with H$_2$O (2×) and brine (2×) and dried over anhydrous sodium sulfate. The crude product was isolated and purified via column chromatography (hexane/ethyl acetate). *Recovery of nitro-substituted aniline*: The aqueous extracts were made basic by addition of 10 M NaOH, and the solution was extracted with CHCl$_3$. The organic solution was washed with H$_2$O and brine (2×) and dried over anhydrous sodium sulfate. Removal of the solvent yielded the nitro-substituted aniline.

Diaryl Ketone Synthesis, General Procedure. Trifluoromethanesulfonic acid (0.35 mL, 4 mmol) was added to a solution of amide **17** (0.24 g, 1 mmol) and the arene (1 mmol) in anhydrous CH$_2$Cl$_2$ (2 mL). The mixture was stirred for 3 h at 50 °C and then poured over ice. The products were extracted into CHCl$_3$, and the organic solution was washed with H$_2$O (2×) and brine (2×) and dried over anhydrous sodium sulfate. The crude product was isolated and purified via column chromatography (hexane/ethyl acetate). Note: ketones **19** and **22** were prepared using the corresponding arene as solvent.

Indanone (13) and Tetralone (15). Trifluoromethanesulfonic acid (0.35 mL, 4 mmol) was added to a solution of amide **7** or **14** (1 mmol) in 1,2-dichlorobenzene (2 mL). The mixture was stirred for 16 h at 60 °C and then poured over ice. The products were extracted into CHCl$_3$, and the organic solution was washed with H$_2$O (2×) and brine (2×) and dried over anhydrous sodium sulfate. The crude product was isolated and purified via column chromatography (hexane/ethyl acetate).

3-Phenyl-*N*-(pyrazin-2-yl)propanamide (1b). Using general procedure A, hydrocinnamoyl chloride (0.88 mL, 5.9 mmol) provided compound **1b** (0.075 g, 0.33 mmol, 6%) as a white solid: mp 83−86 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.77 (t, 2H, *J* = 8.1 Hz), 3.08(t, 2H *J* = 7.8 Hz), 7.21−7.30 (m, 6H), 8.19−8.41 (m, 2H), 9.58 (s, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 31.1, 38.9, 126.5, 128.3, 128.7, 137.1, 140.0, 140.2, 141.9, 148.1, 170.8; LRMS (EI) *m/z* 227, 199, 183, 131, 105, 91, 77. Anal. Calcd for C$_{13}$H$_{13}$N$_3$O: C, 68.71; H, 5.77; N, 18.49. Found: C, 68.58; H, 5.75; N, 18.18.

3-(4-Isopropylphenyl)-*N*-(4-nitrophenyl)propanamide (3). Using general procedure B, 3-(4-isopropylphenyl)propionic acid (0.3 g, 1.6 mmol) provided compound **3** (0.39 g, 1.3 mmol, 81%) as a yellow solid: mp = 122−124 °C; ^{1}HNMR ((CD$_3$)$_2$CO, 300 MHz) δ 1.21(d, 6H, *J* = 6.9 Hz), 2.76(t, 2H, *J* = 8.1 Hz), 2.86(m, 1H), 2.99(t, 2H, *J* = 8.1 Hz), 7.14−7.21 (m, 4H), 7.87−7.92 (m, 2H), 8.18−8.23 (m, 2H), 9.69 (s, 1H); ^{13}C NMR ((CD$_3$)$_2$CO, 300 MHz) δ 23.5, 30.4, 33.5, 38.6, 118.6, 124.7, 126.3, 128.3, 138.4, 142.8, 145.4, 146.5, 171.2; LRMS (EI) *m/z* 312, 295, 267, 254, 226, 159, 147, 133, 117, 105, 91; HRMS C$_{18}$H$_{20}$O$_3$N$_2$ calcd 312.14740, found 312.14578.

N-(4-Nitrophenyl)-3-*p*-tolylpropanamide (4). Using general procedure B, 3-(4-methylphenyl)propionic acid (0.3 g, 1.8 mmol) provided compound **4** (0.33 g, 1.2 mmol, 67%) as a yellow oil: ^{1}H NMR (acetone-*d*$_6$, 300 MHz) δ 2.27 (s, 3H), 2.75 (t, 2H, *J* = 7.5 Hz), 2.96 (q, 2H, *J* = 7.5 Hz), 7.07−7.16(m, 4H), 7.89 (d, 2H, *J* = 9.3 Hz),

8.20 (d, 2H, J = 9.3 Hz), 9.71 (s, 1H); ^{13}C NMR (acetone-d_6, 300 MHz) δ 20.1, 30.4, 38.7, 118.6, 124.7, 128.2, 129.0, 135.3, 138.0, 142.8, 145.4, 171.2; LRMS (EI) m/z 284 (M$^+$), 267, 254, 239, 226, 138, 119, 105, 91; HRMS $C_{16}H_{16}O_3N_2$ calcd 284.11610, found 284.11729.

3-(4-Methoxyphenyl)-N-(4-nitrophenyl)propanamide (5). Using general procedure B, 3-(4-methoxyphenyl)propionic acid (0.1 g, 0.56 mmol) provided compound **5** (0.16 g, 5.3 mmol, 95%) as a yellow solid: mp = 140−143 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.71 (t, 2H, J = 7.5 Hz), 3.02 (t, 2H, J = 7.5 Hz), 3.79 (s, 3H), 6.84 (d, 2H, J = 8.7 Hz), 7.15 (d, 2H, J = 8.4 Hz), 7.59 (s, 1H), 7.63 (d, 2H, J = 9.3 Hz), 8.17 (d, 2H, J = 9.3 Hz); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 30.4, 39.8, 55.3, 113.4, 114.1, 119.0, 125.1, 126.4, 129.3, 132.1, 143.4, 143.6, 158.3, 171.0; HRMS $C_{16}H_{16}O_4N_2$ calcd 300.11101, found 300.10967.

3-(4-Bromophenyl)-N-(4-nitrophenyl)propanamide (6). Using general procedure B, 3-(4-bromophenyl)propionic acid (0.4 g, 1.75 mmol) provided compound **6** (0.47 g, 1.35 mmol, 77%) as a yellow solid: mp = 182−184 °C; ^{1}H NMR (acetone-d_6, 300 MHz) δ 2.78 (t, 2H, J = 7.8 Hz), 3.01 (t, 2H, J = 7.5 Hz), 7.25 (d, 2H, J = 8.4 Hz), 7.45 (d, 2H, J = 8.4 Hz), 7.88 (d, 2H, J = 9.3 Hz), 8.20 (d, 2H, J = 9.3 Hz), 9.72 (s, 1H); ^{13}C NMR (acetone-d_6, 300 MHz) δ 30.1, 38.2, 112.6, 112.7, 118.6, 118.7, 119.4, 124.7, 126.0, 130.5, 131.3, 140.6, 142.8, 145.3, 170.9; LRMS (EI) m/z 350, 290, 211, 183, 171, 138, 122, 104, 90, 77, 63; LRMS (EI) m/z 350/348 (M$^+$), 320/318, 213/211, 1171/169, 138; HRMS $C_{15}H_{13}O_3N_2Br$ calcd 348.01096, found 348.01053.

(E)-N-(4-Nitrophenyl)-4-phenylbut-3-enamide (14). Using general procedure B, styrylacetic acid (0.10 g, 0.62 mmol) provided compound **14** (0.093 g, 0.33 mmol, 53%) as a yellow oil: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.40 (dd, 2H, J = 1, 7.2 Hz), 6.32−6.42 (m, 1H), 6.63−6.68 (m, 1H), 7.27−7.43 (m, 5H), 7.73 (d, 2H, J = 9.3 Hz), 7.87 (s, 1H), 8.20 (d, 2H, J = 9 Hz); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 42.0, 113.4, 119.2, 120.8, 125.1, 126.4, 128.26, 129.0, 136.1, 143.5, 143.6, 169.4; HRMS $C_{16}H_{14}O_3N_2$ calcd 282.10045, found 282.10067.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **1b**, **3−6**, and **14**; computation methods and results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor George A. Olah on the occasion of his 85th birthday.

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