Note

Superelectrophiles in synthesis: preparation of aromatic imides

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Superelectrophiles in synthesis: preparation of aromatic imides.

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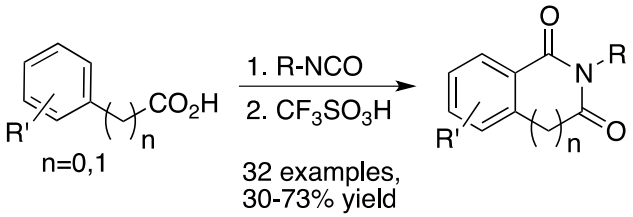
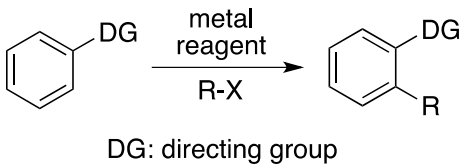


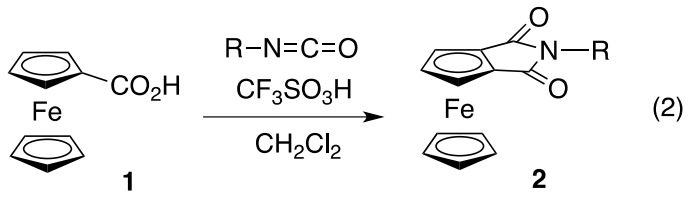
Abstract. Aromatic carboxylic acids are found to undergo reactions with isocyanates wherein triflic acid promotes formation of aromatic imide products in fair to good yields. It is proposed that the carboxylic acid group directs the isocyanate electrophile to the *ortho* position. This is thought to occur by formation of a temporary carbamic acid anhydride group, which cleaves upon *ortho* functionalization. A series of imide products are synthesized, as well as the synthesis of a potential selective inhibitor of tyrosyl DNA phosphodiesterase II.

Functionalized aromatic compounds are important building blocks for a wide variety of fine chemicals, pharmaceutical intermediates, and commodity chemicals.[1] An important strategy for the synthesis of functionalized arenes has involved the use of *ortho* directing groups (eq 1).[2]



(1)

This may involve the metalation of the *ortho*-position on the arene through the use of strongly basic reagents, such as butyllithium, or through the use of catalytic transition metals[3] The metallated *ortho*-position may then be reacted with an electrophilic or nucleophilic reagent, depending on the nature of the coordinating metal. Recently, we reported the superacid-promoted reactions of ferrocenes with isocyanates.[4] When ferrocene carboxylic acids are used, the corresponding ferrocenyl imides are formed in good yields (eq 2). This result suggested to

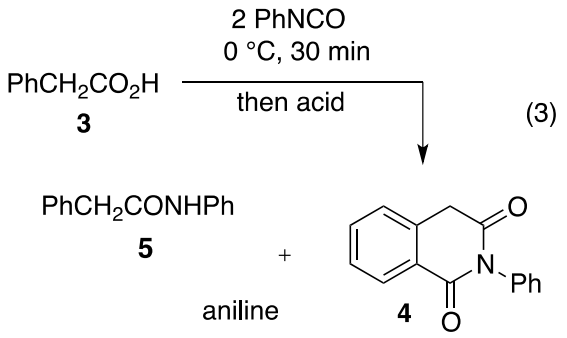


1 **2** (2)

us a potentially new method of directing incoming electrophilic groups to the *ortho* position of an aromatic carboxylic acid: temporary covalent attachment of an electrophile. In the following Note, we describe our efforts to extend this chemistry to aromatic substrates beyond the ferrocene derivatives.

The studies were initiated using phenylacetic acid and phenyl isocycanate. We sought to optimize the conversion to an imide by varying the ratio of carboxylic acid and isocyanate, the reaction time and temperature, the type of acid promoter, and the quantity of acid promoter.

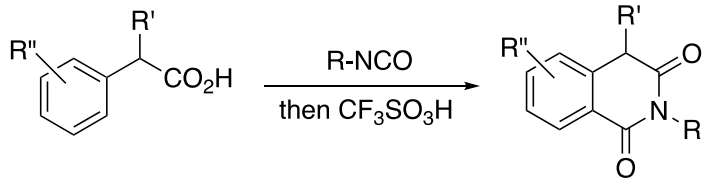
In general, the best conversion to an imide product was obtained by reacting phenylacetic acid (**3**) and phenyl isocycanate – in a 1:1.5 mol ratio – for 30 minutes at 0 °C in CH_2Cl_2 and then adding 10 equivalents of CF_3SO_3H, triflic acid (eq 3). With these reaction conditions, the imide **4** is isolated in 62% yield, but it is also accompanied by ca. 20% of aniline. When only 2 equivalents of triflic acid is used, imide **4** and amide **5** are formed in roughly equal amounts with some aniline formed as a coproduct. With even less triflic acid, no imide is formed and

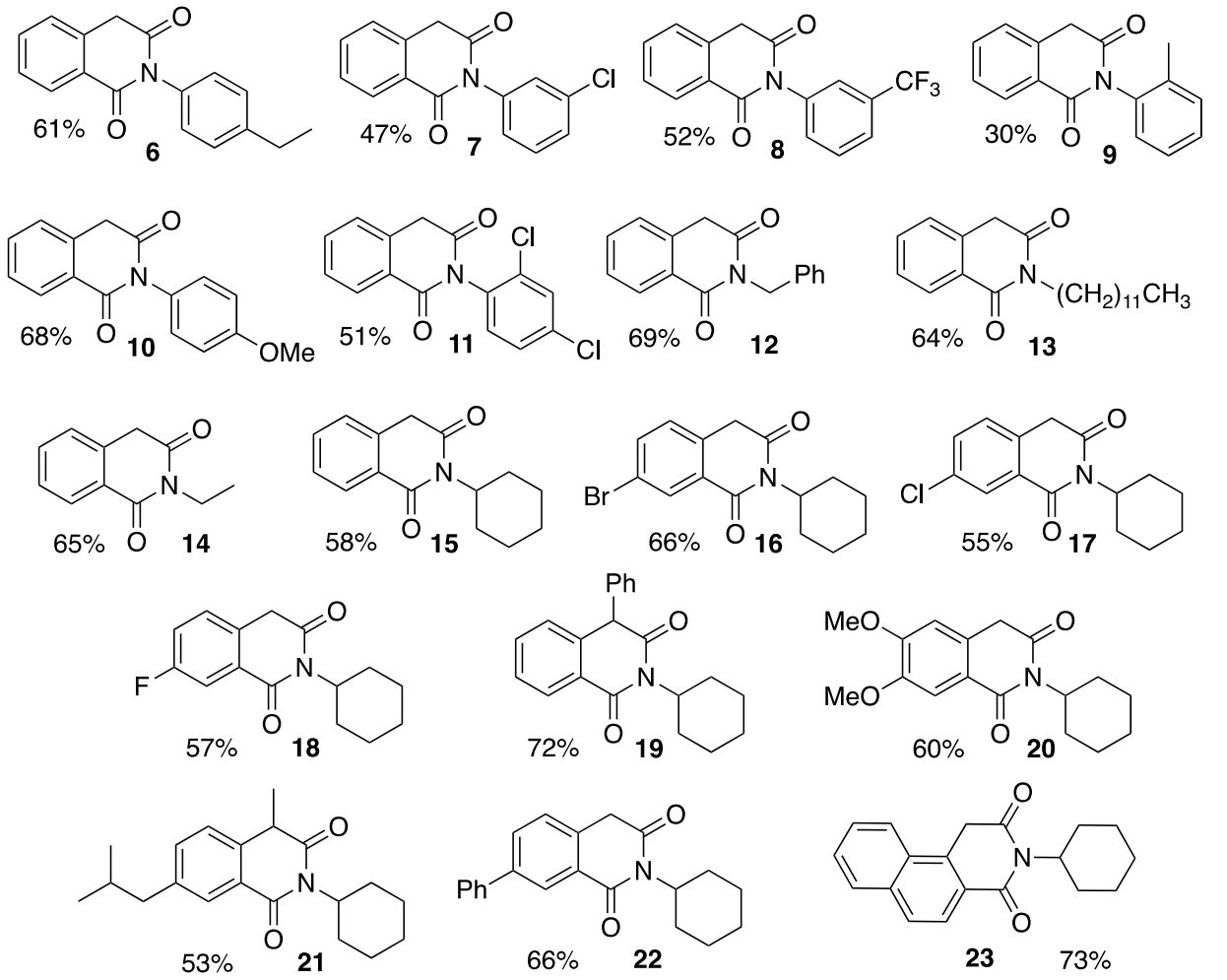


only the amide **5** is observed. If a weaker acid is used, such as H_2SO_4, neither the imide or amide are formed as a major product. Primarily aniline is found in the product mixture.

In order to evaluate the scope of this reaction, a variety of arylacetic acids and isocyanates were subjected to the optimum reaction conditions (Table 1). Using phenylacetic acid, aryl isocyanates or aliphatic isocyanates, the respective aromatic imides (**6-11**) are formed in good yields. The chemistry tolerates substituents on the arylacetic acid. This includes halogens (**16-18**), alkyl groups (**21**), aryl groups (**19** and **22**), ether groups (**20**), and ring-fused derivatives (**23**). When a strongly deactivating substituent is present, however, the chemistry does not proceed to the imide product. For example, 4-nitrophenyl acetic acid was reacted with

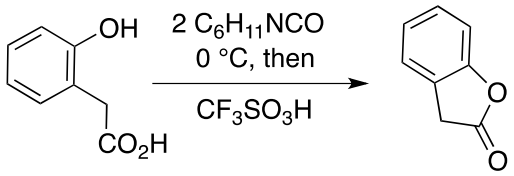
Table 1. Products and yields from the reactions of arylacetic acid derivatives, isocyanates, and triflic acid.





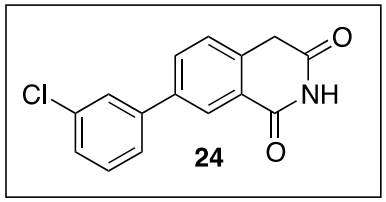
cyclohexyl isocyanate and a complex product mixture was obtained. In some cases, the Friedel-Crafts chemistry was observed at the carboxylic acid group. For example, 3-phenylpropionic

acid leads to 1-indanone as product. It was alsoobserved that other nucleophilic groups may react with the carboxylic acid group. Thus, 2-(2-hydroxyphenyl)acetic acid leads to formation of benzofuran-2(3*H*)-one (eq 4).



(4)

Aromatic imides similar to those obtained (Table 1) have shown biological activities. For example, compound **24** has been examined for its activity as a selective inhibitor of tyrosyl DNA phosphodiesterase II (TDP2).[5] Using the biaryl substrate **25**, the analog **26** is prepared in good yield by reaction with the isocyanate and triflic acid (eq 5).



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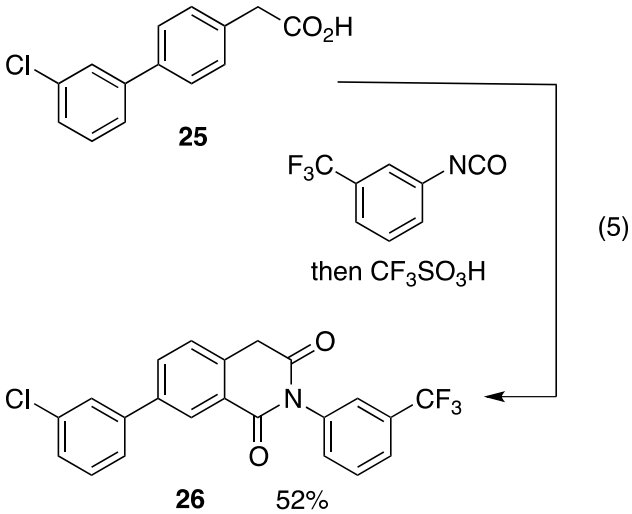
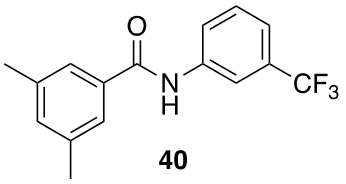


25

26 52%

(5)

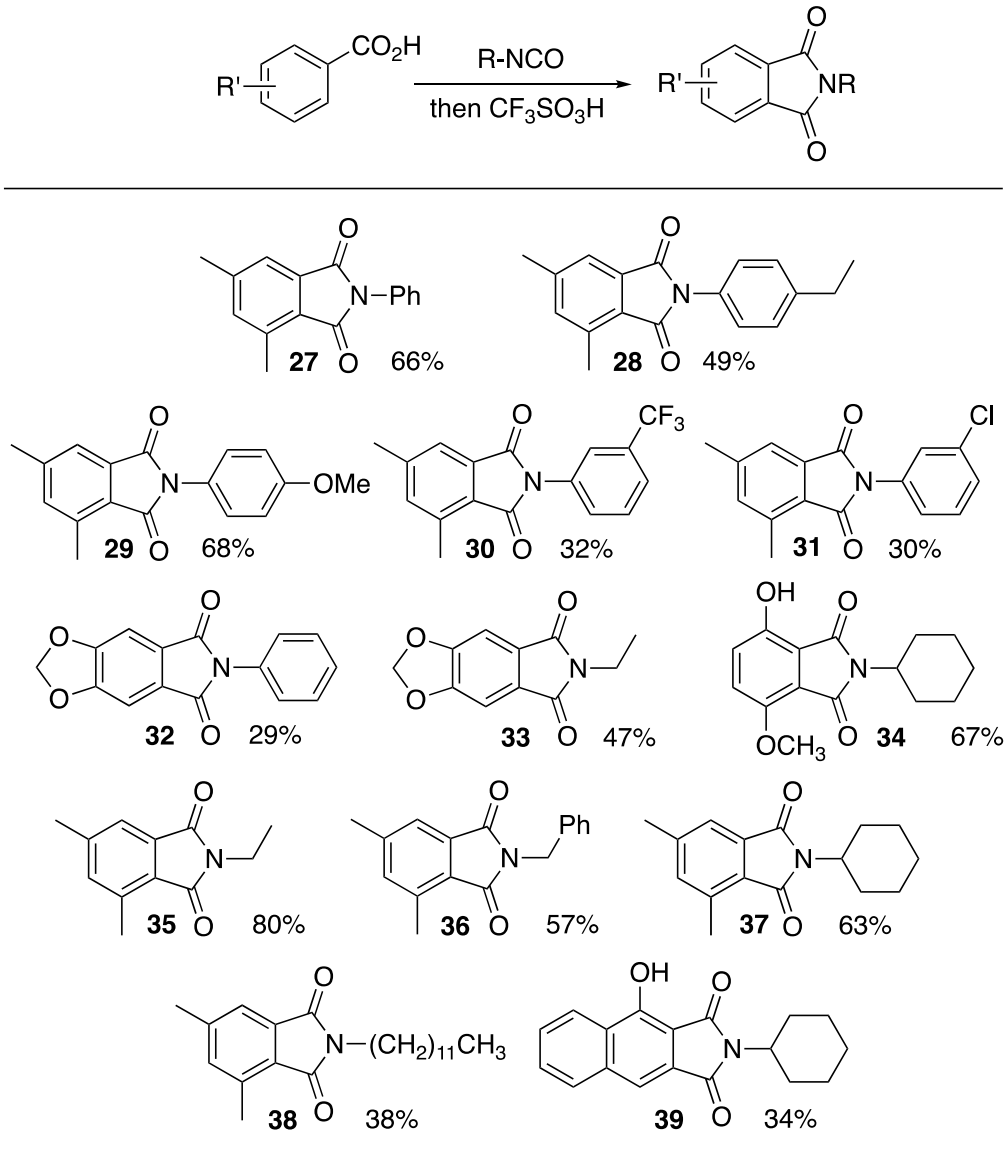
Benzoic acid derivatives provide phthalimides upon reactions with isocyanates and triflic acid (Table 2). With aryl isocyanates, phthalimides (**27-32**) are formed in fair to good yields. It was observed that some of these conversions often give significant amounts of the corresponding benzamide products. For example, product **40** is generated from the reaction of 3,5-dimethylbenzoic acid and 3-trifluoromethylphenylisocyanate. The crude product mixture is found to contain phthalimide (**30**) and benzamide (**40**) in a 73:23 ratio.



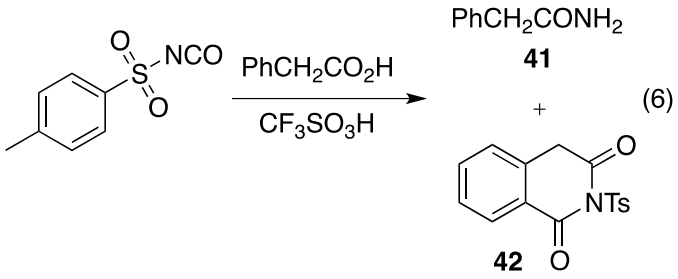
40

Unfortunately, compounds **30** and **40** are difficult to separate using chromatography, so the phthalimide **30** could only be isolated in 32% yield. Likewise, product **31** also had to be separated from an amide contaminant and as a result, the isolated yield of **31** is low. These coproducts are not entirely unexpected, as carboxylic acids and isocyanates are known to provide good yields of amides by decarboxylation of carbamic acid anhydride intermediates (*vide infra*).[6] In addition to the aryl isocyanates, aliphatic-type isocyanates provided the phthalimide products (**33-39**). Phthalimide **34** is isolated in 67% yield as the product from 2,5-dimethoxybenzoic acid. Evidently, one of the methoxy groups is demethylated in the superacid and the phthalimide **34** is formed. A similar process is envisaged to occur to provide compound **39** from 1-methoxynaphthoic acid.

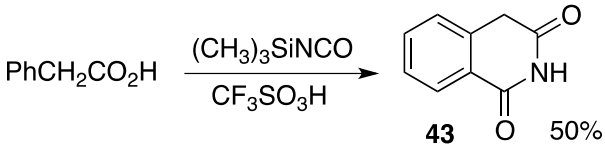
Table 2. Products and isolated yields from the reactions of benzoic acid derivative, isocyanates, and triflic acid.



Given the synthetic value of aromatic imides, we sought to determine if products could be formed with protected and deprotected (unsubstituted) nitrogen centers. Two strategies were attempted: use of trimethylsilylisocyanate and *p*-toluenesulfonyl isocyanate in the cyclization strategy. Using phenylacetic acid, *p*-toluenesulfonyl isocyanate did not provide the desired imide (**42**) but instead the primary amide (**41**) was formed (eq 6). The same type of



(6)

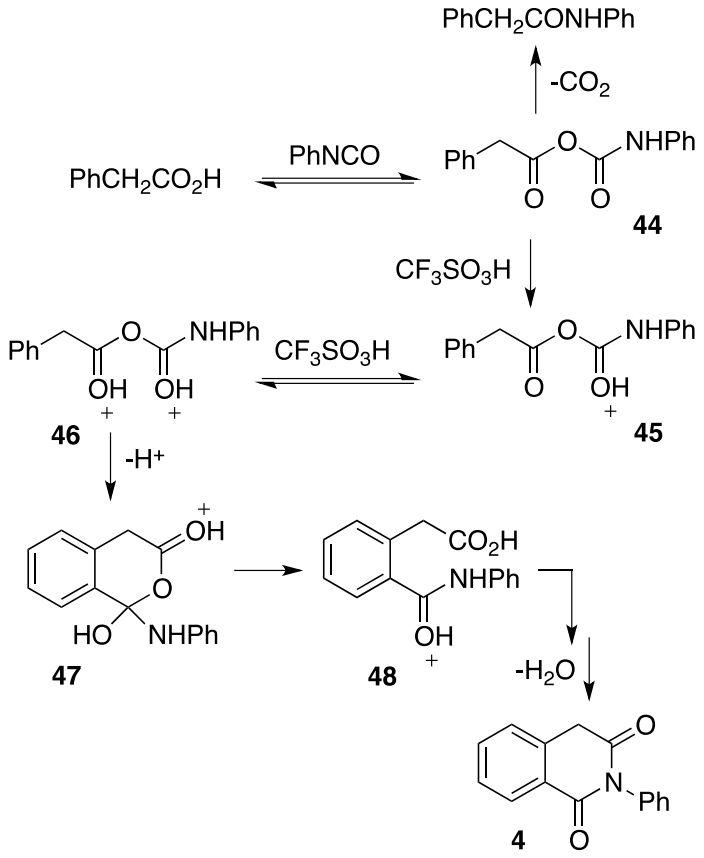


(7)

outcome was observed with 2,5-dimethylbenzoic acid – exclusive formation of the benzamide. With phenylacetic acid and trimethylsilylisocyanate, the unsubstituted aromatic imide (**43**) is isolated in 50% yield (eq 7). Evidently, the silyl group cleaves off in the superacidic media (eq 7). With benzoic acid derivatives, only benzamide products are obtained from trimethylsilylisocyanate.

To explain the transformations in Tables 1 and 2, it is suggested that the isocyanates and carboxylic acids react to provide the carbamic acid anhydrides as the initial intermediate

(Scheme 1). For example, phenylacetic acid reacts with phenyl isocyanate to give the adduct **44**. Previously, this type of species has been proposed as the key intermediate in synthetic



Scheme 1. Proposed mechanism for imide formation.

methodologies leading to amide products.[7] Amides are thought to arise from decarboxylation of carbamic acid anhydrides (such as **44**).[6,7] The results from our study indicate that another reaction manifold is possible with the carbamic acid anhydrides. Protonation leads to the cationic structure **45**. With the need for excess triflic acid in the conversions, this is consistent with the formation of diprotonated, superelectrophilic species (**46**).[8] In several previous studies, doubly protonated species have been proposed with dicarbonyl compounds in triflic acid-

promoted reactions.[9] Superelectrophile **46** should be capable of undergoing the intramolecular Friedel-Crafts-type reaction, leading to intermediate **47**. Ring-opening to **48** then provides the observed product **4** by dehydration. The proposed mechanism may suggest why excess superacid is necessary for the conversion. First, the protonated carbamic acid anhydrides may be less prone to undergo decarboxylations to form the amides. Secondly, the superacid is likely needed to generate the reactive, diprotonated species **46**.

In summary, we have found that aromatic carboxylic acids undergo reactions with isocyanates - and with the addition of triflic acid - aromatic imides are directly formed. Aryl acetic acids and benzoic acids have been found to produce the aromatic imides by this chemistry. We believe the conversion involves formation of a carbamic acid anhydride intermediate which then undergoes a superelectrophilic C-C bond formation. The overall transformation represents the use of a temporary covalent attachment of two functional groups – the carboxylic acid and isocyanate – to effect *ortho*-functionalization on the arene.

EXPERIMENTAL SECTION

General. All reactions were performed under an argon atmosphere using oven dried glassware. Trifluoromethanesulfonic acid (triflic acid) was freshly distilled prior to use. All commercially available compounds and solvents were used as received. ^{1}H and $^{13}C\{^{1}H\}$ NMR were done using either 300 MHz or 500 MHz spectrometers. Low-resolution mass spectra were obtained from a gas chromatography instrument quipped with a mass-selective detector and electron impact ionization. High resolution mass spectra were obtained on a Bruker maXis II Q-TOF LC/MS.

General procedure for the synthesis of aromatic imides. The carboxylic acid (0.5 mmol) is dissolved in 5 mL CH_2Cl_2 at room temperature under an N_2 atmosphere. The isocyanate (0.75 mmol, 1.5 equiv.) is added via syringe and the reaction is stirred for 30 minutes. Trifluoromethanesulfonic acid (0.5 mL, 0.44 mmol, approx. 10 eq) is then added and the solution is stirred for 2 hours. The mixture is quenched by pouring the solution onto 20 g of ice and the resulting biphasic mixture is adjusted to pH 10-11 with saturated Na_2CO_3(aq). After transferring to a separatory funnel, the organic layer is separated and the aqueous layer is extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts are subsequently washed with deionized water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate, and filtered. The solvent is removed by rotary evaporation and the crude product purified by flash chromatography on silica gel.

2-Phenylisoquinoline-1,3(2H,4H)-dione (4).[10] Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and phenylisocyanate (0.082 mL, 89 mg, 0.75 mmol) provide imide **4** as a white solid (73 mg, 0.31 mmol, 62%), R_f = 0.47 (2:1 hexanes/ethyl acetate), mp 179 - 181 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.65 (m, 1H), 7.55 – 7.50 (m, 4H), 7.37 (d, *J* = 7.0 Hz, 1H), 7.24 – 7.22 (m, 2H), 4.24 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.0, 165.1, 135.1, 134.2, 134.0, 129.5, 129.4, 128.7, 128.5, 127.9, 127.3, 125.5, 37.0. HRMS (ESI): Calcd. for $C_{15}H_{12}NO_2$ ($[M+H]^+$) m/z 238.0868, found m/z 238.0872.

2-(4-ethylphenyl)isoquinoline-1,3(2H,4H)-dione (6).[11] Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and 4-ethylphenyl isocyanate (0.108 mL,110 mg, 0.75

mmol) provide imide **6** as a white solid (81 mg, 0.31 mmol, 61%), R_f = 0.66 (75:25 hexanes/ethyl acetate), mp 129 – 131 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.1 Hz, 1H), 7.64 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.38 – 7.32 (m, 3H), 7.13 (d, *J* = 8.2 Hz, 2H), 4.22 (s, 2H), 2.74 (q, *J* = 7.7 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.0, 165.1, 144.7, 134.2, 133.9, 132.5, 129.5, 128.8, 128.2, 127.8, 127.3, 125.5, 36.9, 28.6, 15.2; HRMS (ESI): Calcd. for $C_{17}H_{15}NO_2Na$ ([M+Na]$^+$) m/z 288.1000, found m/z 288.0999.

2-(3-Chlorophenyl)isoquinoline-1,3(2H,4H)-dione (7).[11] Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and 3-chlorophenyl isocyanate (0.091 mL, 115 mg, 0.75 mmol) provides imide **7** as a white solid (64 mg, 0.24 mmol, 47%), R_f = 0.25 (75:25 hexanes/ethyl acetate), mp 156 – 158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 7.9 Hz, 1H), 7.67 (ddd, *J* = 7.6, 7.5, 1.0 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.47 – 7.43 (m, 2H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.26 (s, 1H), 7.16 – 7.12 (m, 1H), 4.23 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.7, 164.8, 136.2, 134.8, 134.2, 134.1, 130.2, 129.5, 129.1, 129.0, 128.0, 127.4, 127.0, 125.2, 36.9; HRMS (ESI): Calcd. for $C_{15}H_{10}ClNO_2Na$ ([M+Na]$^+$) m/z 294.0298, found m/z 294.0293.

2-(3-(Trifluoromethyl)phenyl)isoquinoline-1,3(2H,4H)-dione (8). Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and 3-(trifluoromethyl)phenyl isocyanate (0.103 mL, 140 mg, 0.75 mmol) provide imide **8** as a white solid (79 mg, 0.26 mmol, 52%), R_f = 0.44 (75:25 hexanes/ethyl acetate), mp 131 – 133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.55 – 7.49 (m, 2H), 7.44 (d, 7.8 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 4.24 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.7, 164.9, 135.6, 134.3, 134.1,

132.3, 131.8 (q, *J* = 33.0 Hz), 129.9, 129.5, 128.0, 127.4, 125.9 (q, *J* = 3.7 Hz), 125.6 (q, *J* = 3.6 Hz), 125.1, 123.7 (q, *J* = 271.8 Hz), 36.9. HRMS (ESI): Calcd. for $C_{16}H_{10}F_3NO_2Na$ ($[M+Na]^+$) m/z 328.0562, found m/z 328.0561.

2-(*o*-Tolyl)isoquinoline-1,3(2H,4H)-dione (9). Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and *o*-tolyl isocyanate (0.093 mL, 100 mg, 0.75 mmol) provide imide **9** as a light brown oil (37.6 mg, 0.15 mmol, 30%), R_f = 0.37 (75:25 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 7.9 Hz, 1H), 7.68 (ddd, *J* = 7.8, 7.6, 1.2 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.41 – 7.34 (m, 4H), 7.14 (d, *J* = 7.5 Hz, 1H), 4.25 (s, 2H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 169.6, 164.7, 135.8, 134.4, 134.0, 131.0, 129.5, 129.1, 128.5, 127.9, 127.4, 127.1, 125.4, 36.9, 17.6. HRMS (ESI): Calcd. for $C_{16}H_{14}NO_2$ ($[M+H]^+$) m/z 252.1024, found m/z 252.1016.

2-(4-Methoxyphenyl)isoquinoline-1,3(2H,4H)-dione (10).[12] Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and 4-methoxyphenyl isocyanate (0.097 mL, 112 mg, 0.75 mmol) provide imide **10** as a white solid (91 mg, 0.34 mmol, 68%), R_f = 0.32 (2:1 hexanes/ethyl acetate), mp 175 - 177 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.66 (ddd, *J* = 7.6, 7.5, 1.3 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.38 – 7.34 (m, 1H), 7.16 – 7.12 (m, 2H), 7.06 – 7.02 (m, 2H), 4.24 (s, 2H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 170.2, 165.2, 159.6, 134.2, 133.9, 129.5, 129.4, 127.9, 127.5, 127.3, 125.5, 114.7, 55.5, 37.0; HRMS (ESI): Calcd. for $C_{16}H_{14}NO_3$ ($[M + H]^+$) m/z 268.0973, found m/z 268.0971.

2-(2,4-Dichlorophenyl)isoquinoline-1,3(2H,4H)-dione (11).[13] Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and 2,4-dichlorophenyl isocyanate (141 mg, 0.75 mmol) provide imide **11** as a white solid (78 mg, 0.26 mmol, 51%), R_f = 0.40 (75:25 hexanes/ethyl acetate), 165 – 167 mp °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, *J* = 7.8 Hz, 1H), 7.69 (ddd, J = 7.6, 7.5, 1.2 Hz, 1H), 7.59 (d, *J* = 2.1 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.43 – 7.37 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 4.33 – 4.20 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.1, 164.1, 135.6, 134.3, 134.2, 133.7, 131.9, 131.3, 130.2, 129.6, 128.2, 128.0, 127.5, 124.9, 36.8; HRMS (ESI): Calcd. for $C_{15}H_{10}Cl_2NO_2$ ($[M + H]^+$) m/z 306.0088, found m/z 306.0083.

2-Benzylisoquinoline-1,3(2H,4H)-dione (12).[14] Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and benzyl isocyanate (0.093 mL, 100 mg, 0.75 mmol) provides imide **12** as a white solid (87 mg, 0.35 mmol, 69%), R_f = 0.33 (80:20 hexanes/ethyl acetate), mp 118 - 120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7.83, 1H), 7.56 (ddd, *J* = 7.6, 7.5, 0.9 Hz, 1H), 7.50 – 7.40 (m, 3H), 7.34 – 7.21 (m, 4H), 5.18 (s, 2H), 4.04 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.8, 164.8, 137.1, 134.1, 133.6, 129.2, 128.9, 128.4, 127.7, 127.5, 127.1, 125.4, 43.3, 36.5; HRMS (ESI): Calcd. for $C_{16}H_{14}NO_2$ ($[M + H]^+$) m/z 252.1024, found m/z 252.1022.

2-Dodecylisoquinoline-1,3(2H,4H)-dione (13). Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and dodecyl isocyanate (0.181 mL, 159 mg, 0.75 mmol) provide imide **13** as a colorless oil (105 mg, 0.32 mmol, 64%), R_f = 0.80 (80:20 hexanes/ethyl acetate), mp 52 - 54 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (dd, *J* = 7.8, 0.5 Hz, 1H), 7.58 (td, *J* = 7.5, 1.2 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 4.03 (s, 2H), 3.98 (t, *J* = 7.7 Hz, 2H), 1.62 (p, *J* = 7.5 Hz, 2H),

1.40 – 1.22 (m, 18H), 0.89 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 169.9, 164.8, 134.1, 133.5, 129.1, 127.6, 127.1, 125.5, 40.3, 36.4, 31.9, 29.63, 29.61, 29.58, 29.53, 29.32, 28.0, 27.1, 22.7, 14.1. HRMS (ESI): Calcd. for $C_{21}H_{32}NO_2$ ($[M + H]^+$) m/z 330.2433, found m/z 330.2430.

2-Ethylisoquinoline-1,3(2H,4H)-dione (14).[15] Using the general procedure, phenylacetic acid (68 mg, 0.5 mmol) and ethyl isocyanate (0.059 mL, 53 mg, 0.75 mmol) provide imide **14** as a white solid (61 mg, 0.33 mmol, 65%), R_f = 0.57 (75:25 hexanes/ethyl acetate), mp 100 – 102 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.8Hz, 1H), 7.54 (ddd, *J* = 7.5, 7.4, 1.3 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 4.04 – 3.95 (m, 4H, 2 CH_2), 1.19 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.7, 164.5, 134.1, 133.4, 129.0, 127.6, 127.0, 125.5, 36.4, 35.2, 13.2; HRMS (ESI): Calcd. for $C_{11}H_{12}NO_2$ ($[M + H]^+$) m/z 190.0868, found m/z 190.0864.

2-Cyclohexylisoquinoline-1,3(2H,4H)-dione (15).[16] Phenylacetic acid (680 mg, 5 mmol) is dissolved in 50 mL CH_2Cl_2 and cyclohexyl isocyanate (0.96 mL, 7.5 mmol, 1.5 eq) is added via syringe. The solution is stirred for 30 min at 25 °C. Trifluoromethanesulfonic acid (3 mL, 33 mmol, 6.6 eq) is slowly added, and after 2 h, the mixture is quenched by pouring it over20 g of ice. The resulting biphasic mixture is adjusted to pH 10-11 with saturated Na_2CO_3 and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts are subsequently washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate, and then filtered. The solvent is removed by rotary evaporation and the crude product is purified by flash chromatography on silica gel to afford a white solid (706 mg, 2.9 mmol, 58%), R_f = 0.8 (80:20 hexanes/ethyl

acetate), mp 157 – 159 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.57 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 7.44 (ddd, *J* = 7.6, 7.5, 0.8 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 4.80 (tt, *J* = 12.3, 3.7 Hz, 1H), 4.01 (s, 2H), 2.41 (qd, *J* = 12.7, 3.6 Hz, 2H), 1.89 – 1.82 (m, 2H), 1.73 – 1.61 (m, 3H), 1.40 (qt, *J* = 13.3, 3.3 Hz, 2H), 1.28 (qt, *J* = 13.0, 3.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 170.5, 165.3, 134.1, 133.3, 129.1, 127.6, 126.8, 126.1, 53.7, 37.2, 29.1, 26.5, 25.4; HRMS (ESI): Calcd. for $C_{15}H_{18}NO_2$ ($[M + H]^+$) m/z 244.1337, found m/z 244.1335.

7-Bromo-2-cyclohexylisoquinoline-1,3(2H,4H)-dione (16). Using the general procedure, 4-bromophenyl acetic acid (108 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **16** as a white solid (106 mg, 0.33 mmol, 66%), R_f = 0.66 (75:25 hexanes/ethyl acetate), mp 103 - 105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, *J* = 2.1 Hz, 1H), 7.65 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 4.75 (tt, *J* = 12.3, 3.7 Hz, 1H), 3.94 (s, 2H), 2.36 (dq, *J* = 12.3, 3.5 Hz, 2H), 1.87 – 1.80 (m, 2H), 1.70 – 1.59 (m, 3H), 1.37 (qt, *J* = 13.2, 3.3 Hz, 2H), 1.30 – 1.20 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 169.8, 164.0, 136.2, 132.8, 131.9, 128.5, 127.8, 121.5, 53.9, 36.8, 29.0, 26.4, 25.3. HRMS (ESI): Calcd. for $C_{16}H_{18}BrNO_4Na$([M + H][CHOONa]$^+$) m/z 390.0317, found m/z 390.0310.

7-Chloro-2-cyclohexylisoquinoline-1,3(2H,4H)-dione (17). Using the general procedure, 4-chlorophenyl acetic acid (85 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **17** as a white solid (76 mg, 0.275 mmol, 55%), R_f = 0.45 (80:20 hexanes/ethyl acetate), mp 107 - 109 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 2.2 Hz, 1H), 7.51 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 4.77 (tt, *J* = 12.3, 3.7 Hz, 1H), 3.97 (s, 2H),

2.37 (qd, *J* = 12.4, 3.7 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.71 – 1.60 (m, 3H), 1.38 (qt, *J* = 13.1, 3.1 Hz, 2H), 1.30 – 1.23 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 169.8, 164.1, 133.8, 133.4, 132.3, 128.9, 128.3, 127.6, 53.9, 36.7, 28.9, 26.4, 25.3. HRMS (ESI): Calcd. for $C_{15}H_{16}ClNO_2Na$ ([M + Na]$^+$) m/z 300.0767, found m/z 300.0754.

2-Cyclohexyl-7-fluoroisoquinoline-1,3(2H,4H)-dione (18). Using the general procedure, 4-fluorophenyl acetic acid (77 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **18** as a white solid (75 mg, 0.28 mmol, 57%), R_f = 0.45 (80:20 hexanes/ethyl acetate), mp °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.30 – 7.21 (m, 2H), 4.77 (tt, *J* = 12.3, 3.7 Hz, 1H), 3.97 (s, 2H), 2.37 (qd, *J* = 12.4, 3.7 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.71 – 1.60 (m, 3H), 1.38 (qt, *J* = 13.1, 3.1 Hz, 2H), 1.30 – 1.23 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 170.1, 164.28 (d, *J* = 2.5 Hz), 161.9 (*J* = 247.3 Hz), 129.76 (*J* = 3.1 Hz), 128.7 (d, *J* = 7.4 Hz), 127.9 (d, *J* = 7.7 Hz), 120.9 (d, *J* = 22.6 Hz), 115.3 (d, *J* = 23.5 Hz), 53.9, 36.6, 29.0, 26.4, 25.3. HRMS (ESI): Calcd. for $C_{15}H_{16}FNO_2Na$ ([M + Na]$^+$) m/z 284.1063, found m/z 284.1055.

2-Cyclohexyl-4-phenylisoquinoline-1,3(2H,4H)-dione (19). Using the general procedure, diphenyl acetic acid (106 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **19** as a white solid (115 mg, 0.36 mmol, 72%), R_f = 0.5 (90:10 hexanes/ethyl acetate), mp 138 – 140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.55 (ddd, *J* = 7.5, 7.4, 1.4 Hz, 1H), 7.48 (ddd, *J* = 7.8, 7.6, 0.9 Hz, 1H), 7.34 – 7.26 (m, 4H), 7.16 – 7.13 (m, 3H), 5.04 (s, 1H), 4.72 (tt, *J* = 12.3, 3.7 Hz, 1H), 2.39 (dq, *J* = 12.4, 3.7 Hz, 1H),

2.26(dq, *J* = 12.4, 3.7 Hz, 1H), 1.84 – 1.77 (m, 2H), 1.69 – 1.62 (m, 2H), 1.53 – 1.45 (m, 1H), 1.40 – 1.20 (m, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 172.4, 165.2, 139.0, 138.0, 133.6, 129.1, 128.9, 128.1, 127.91, 127.89, 127.88, 126.2, 54.1, 53.6, 29.6, 28.3, 26.5, 26.3, 25.3. HRMS (ESI): Calcd. for $C_{21}H_{22}NO_2$ ($[M + H]^+$) m/z 320.1650, found m/z 320.1646.

2-Cyclohexyl-6,7-dimethoxyisoquinoline-1,3(2H,4H)-dione (20). Using the general procedure, 3,4-dimethoxyphenyl acetic acid (98 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **20** as a yellow solid (91 mg, 0.3 mmol, 60%), R_f = 0.18 (80:20 hexanes/ethyl acetate), mp 155 – 157 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (s, 1H), 6.61 (s, 1H), 4.75 (tt, *J* = 12.1, 3.6 Hz, 1H), 3.93 (s, 6H), 3.91 (s, 2H), 2.37 (qd, *J* = 12.3, 3.5 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.69 – 1.58 (m, 3H), 1.36 (qt, *J* = 13.1, 3.2 Hz, 2H), 1.28 – 1.20 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 170.6, 165.1, 153.7, 148.7, 128.3, 118.7, 110.2, 108.3, 56.2, 56.1, 53.5, 39.9, 29.1, 26.5, 25.4. HRMS (ESI): Calcd. for $C_{17}H_{21}NO_4Na$ ($[M + Na]^+$) m/z 326.1368, found m/z 326.1365.

7-Isobutyl-4-methyl-2-phenylisoquinoline-1,3(2H,4H)-dione (21). Using the general procedure, α-methyl-4-(isobutyl)phenyl acetic acid (103 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **21** as a white solid (81 mg, 0.27 mmol, 53%), R_f = 0. (80:20 hexanes/ethyl acetate), mp 133 – 135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 1.6 Hz, 1H), 7.56 – 7.52 (m, 2H), 7. 50 – 7.46 (m, 2H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.21 (m, 2H), 4.08 (q, *J* = 7.5 Hz, 1H), 2.61 (d, *J* = 7.2 Hz, 2H), 1.96 (sept, *J* = 6.8 Hz, 1H), 1.79 (d, *J* = 7.5 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 174.5, 165.0, 141.5, 137.9, 135.5, 135.2,

129.5, 129.3, 128.6, 128.5, 126.6, 124.4, 44.8, 41.4, 30.1, 22.4, 22.3; HRMS (ESI): Calcd. for $C_{20}H_{21}NO_2Na$ ([M + Na]$^+$) m/z 330.1470, found m/z 330.1465.

2-Cyclohexyl-7-phenylisoquinoline-1,3(2H,4H)-dione (22). Using the general procedure, 4-biphenyl acetic acid (106 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **22** as a white solid (105 mg, 0.33 mmol, 66%), R_f = 0.38 (90:10 hexanes/ethyl acetate), mp 159 – 161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (d, *J* = 1.8 Hz, 1H), 7.77 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.50 – 7.34 (m, HH), 7.80 (d, *J* = 8.0 Hz, 1H), 4.82 (tt, *J* = 12.2, 3.6 Hz, 1H), 4.01 (s, 2H), 2.43 (qd, *J* = 12.2, 3.1 Hz, 2H), 1.89 – 1.83 (m, 2H), 1.72 – 1.63 (m, 3H), 1.48 – 1.24 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.4, 165.3, 140.7, 139.5, 132.9, 131.9, 129.0, 127.9, 127.4, 127.3, 127.0, 126.5, 53.8, 37.0, 29.0, 26.5, 25.4. HRMS (ESI): Calcd. for $C_{21}H_{22}NO_2$ ([M + H]$^+$) m/z 320.1650, found m/z 320.1646.

3-Cyclohexylbenzo[*f*]isoquinoline-2,4(1H,3H)-dione (23). Using the general procedure, 1-naphthaleneacetic acid (93 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **23** as a white solid (107 mg, 0.37 mmol, 73%), R_f = 0.42 (90:10 hexanes/ethyl acetate), mp 166 - 168 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.8 Hz, 1H), 7.91 – 7.88 (m, 2H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.67 – 7.61 (m, 2H), 4.87 (tt, *J* = 12.3, 3.7 Hz, 1H), 4.27 (s, 2H), 2.47 (dq, *J* = 12.3, 3.4 Hz, 2H), 1.92 – 1.85 (m, 2H), 1.75 – 1.67 (m, 3H), 1.43 (tq, *J* = 13.0, 3.1 Hz, 2H), 1.31 (tq, *J* = 12.8, 3.4 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.1, 165.6, 135.2, 132.5, 129.3, 128.9, 128.7, 127.9, 127.4, 124.0, 123.7, 123.4, 53.7, 34.8, 29.1, 26.5, 25.4. HRMS (ESI): Calcd. for $C_{19}H_{20}NO_2$ ([M + H]$^+$) m/z 294.1494, found m/z 294.1489.

7-(3-Chlorophenyl)-2-(3-(trifluoromethyl)phenyl)isoquinoline-1,3(2H,4H)-dione (26). Using the general procedure, (3'-chloro[1,1'-biphenyl]-4-yl)acetic acid (123 mg, 0.5 mmol) and 3-trifluoromethylphenyl isocyanate (0.103 mL, 140 mg, 0.75 mmol) provide imide **26** as a white solid (108 mg, 52%), R_f = 0.18 (80:20 hexanes/ethyl acetate), mp 150 - 152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (d, *J* = 1.9 Hz, 1H), 7.88 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.70-7.65 (m, 1H), 7.65 – 7.63 (m, 1H), 7.56 – 7.52 (m, 2H), 7.49 – 7.39 (m, 4H), 4.30 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.5, 164.7, 141.0, 139.9, 135.5, 135.0, 133.4, 132.9, 132.7, 132.2 131.8 (q, *J* = 33 Hz), 130.4, 130.3, 130.0, 129.8, 128.2, 128.1, 127.8, 127.7, 127.3, 127.2, 126.0, 125.9, 125.7, 125.3, 125.25, 125.19, 123.7 (q, *J* = 272 Hz), 36.7. HRMS (ESI): Calcd. for $C_{22}H_{13}ClF_3NO_2Na$ ($[M + Na]^+$) m/z 438.0485, found m/z 438.0482.

4,6-Dimethyl-2-phenylisoindoline-1,3-dione (27).[17] Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and phenyl isocyanate (0.082 mL, 89.3 mg, 0.75 mmol) provide imide **27** as a white solid (83 mg, 0.33 mmol, 66%), R_f = 0.44 (80:20 hexanes/ethyl acetate), mp 116 - 119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.54 – 7.49 (m, 2H), 7.47 – 7.43 (m, 2H), 7.41 (tt, *J* = 7.3, 1.1 Hz, 1H), 7.35 (s, 1H), 2.72 (s, 3H), 2.50 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.0, 167.5, 145.1, 138.7, 137.2, 132.6, 131.9, 129.0, 127.8, 126.6, 125.9, 122.0, 21.8, 17.6; HRMS (ESI): Calcd. for $C_{16}H_{14}NO_2$ ($[M + H]^+$) m/z 252.1024, found m/z 252.1020.

2-(4-Ethylphenyl)-4,6-dimethylisoindoline-1,3-dione (28). Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and 4-ethylphenyl isocyanate (0.108 mL, 110 mg, 0.75 mmol) provide imide **28** as a white solid (68 mg, 0.25 mmol, 49%), R_f = 0.52 (90:10 hexanes/ethyl acetate), mp 131 – 133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.36 – 7.29 (m, 5H), 2.71 (q, *J* = 7.7 Hz, 2H), 2.69 (s, 3H), 2.48 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.2, 167.6, 145.0, 144.0, 138.1, 137.1, 132.7, 129.4, 128.5, 126.5, 126.0, 121.9, 28.6, 21.8, 17.6, 15.4. HRMS (ESI): Calcd. for $C_{18}H_{18}NO_2$ ([M + H]$^+$) m/z 280.1337, found m/z 280.1334.

2-(4-Methoxyphenyl)-4,6-dimethylisoindoline-1,3-dione (29). Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and 4-methoxyphenyl isocyanate (0.097 mL, 112 mg, 0.75 mmol) provide imide **29** as a white solid (95 mg, 0.34 mmol, 68%), R_f = 0.20 (90:10 hexanes/ethyl acetate), mp 157 - 159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.35 (s, 1H), 7.33 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 2.71 (s, 3H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.3, 167.8, 159.1, 145.0, 138.2, 137.1, 132.7, 128.0, 126.0, 124.6, 121.9, 114.4, 55.5, 21.8, 17.6. HRMS (ESI): Calcd. for $C_{17}H_{16}NO_3$ ([M + H]$^+$) m/z 282.1130, found m/z 282.1128.

4,6-Dimethyl-2-(3-(trifluoromethyl)phenyl)isoindoline-1,3-dione (30). Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and 3-(trifluoromethyl)phenyl isocyanate (0.103 mL, 140 mg, 0.75 mmol) provide imide **30** as a white solid (51 mg, 0.16 mmol, 32%), R_f = 0.68 (75:25 hexanes/ethyl acetate), mp 111 – 113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ

7.80 (s, 1H), 7.72 – 7.68 (m, 1H), 7.68 – 7.63 (m, 2H), 7.62 (s, 1H) 7.38 (s, 1H), 2.73 (s, 3H), 2.53 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 167.6, 167.0, 145.6, 138.6, 137.6, 132.5, 132.3, 131.5 (q, *J* = 32.9 Hz), 129.7, 129.5, 125.7, 124.4 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.6 Hz), 123.4 (q, *J* = 3.9 Hz), 122.2, 21.9, 17.7. HRMS (ESI): Calcd. for $C_{17}H_{13}F_3NO_2$ ($[M + H]^+$) m/z 320.0898, found m/z 320.0893. Chromatography purification also provides by-product amide **40**.

2-(3-Chlorophenyl)-4,6-dimethylisoindoline-1,3-dione (31). Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and 3-chlorophenyl isocyanate (0.091 mL, 115 mg, 0.75 mmol) provide imide **31** as a white solid (43 mg, 0.15 mmol, 30%), R_f = 0.75 (75:25 hexanes/ethyl acetate), mp 168 – 171 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.52 – 7.50 (m, 1H), 7.47 – 7.42 (m, 1H), 7.40 – 7.35 (m, 3H), 2.72 (s, 3H), 2.52 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 167.6, 167.1, 145.4, 138.5, 137.5, 134.5, 133.0, 132.4, 129.9, 127.9, 126.7, 125.7, 124.6, 122.2, 21.9, 17.7. HRMS (ESI): Calcd. for $C_{16}H_{13}ClNO_2$ ($[M + H]^+$) m/z 286.0635, found m/z 286.0630.

6-Phenyl-5H-[1,3]dioxolo[4,5-f]isoindole-5,7(6H)-dione (32).[17] Using the general procedure, piperonylic acid (83 mg, 0.5 mmol) and phenyl isocyanate (0.082 mL, 89.3 mg, 0.75 mmol) provide imide **32** as a white solid (39 mg, 0.15 mmol, 29%), R_f = 0.19 (90:10 hexanes/ethyl acetate), mp 214 – 217 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 – 7.48 (m, 2H), 7.47 – 7.37 (m, 3H), 7.32 (s, 2H), 6.21 (s, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 166.7, 153.0, 131.9, 129.0, 127.9, 127.3, 126.4, 104.0, 103.1; HRMS (ESI): Calcd. for $C_{15}H_9NO_4Na$ ($[M + Na]^+$) m/z 290.0429, found m/z 290.0424.

6-Ethyl-*5H*-[1,3]dioxolo[4,5-f]isoindole-5,7(6H)-dione (33). Using the general procedure, piperonylic acid (83 mg, 0.5 mmol) and ethyl isocyanate (0.059 mL, 53.3 mg, 0.75 mmol) provide imide **33** as a white solid (51 mg, 0.24 mmol, 47%), R_f = 0.30 (90:10 hexanes/ethyl acetate), mp 161 – 163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (s, 2H), 6.14 (s, 2H), 3.65 (q, *J* = 7.3 Hz, 2H), 1.22 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 137.6, 152.4, 127.7, 103.6, 102.9, 32.9, 14.0. HRMS (ESI): Calcd. for $C_{11}H_{10}NO_4$ ($[M + H]^+$) m/z 220.0610, found m/z 220.0605.

2-Cyclohexyl-4-hydroxy-7-methoxyisoindoline-1,3-dione (34). Using the general procedure, 2,5-dimethoxybenzoic acid (91 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **34** as a white solid (92 mg, 0.34 mmol, 67%), R_f = 0.20 (2:1 hexanes/ethyl acetate), mp 148 - 150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 3.1 Hz), 7.23 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.16 (d, *J* = 9.0 Hz, 1H), 4.82 (tt, *J* = 12.1, 3.6 Hz, 1H), 3.87 (s, 3H), 2.40 (qd, *J* = 12.3, 3.7 Hz, 2H), 1.92 – 1.85 (m, 2H), 1.75 – 1.68 (m, 3H), 1.42 (qt, *J* = 13.2, 3.4 Hz, 2H), 1.27 (qt, *J* = 13.2, 3.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 161.1, 156.7, 147.5, 147.0, 124.5, 117.5, 114.8, 108.7, 56.0, 55.3, 28.5, 26.2, 25.1. HRMS (ESI): Calcd. for $C_{15}H_{18}NO_4$ ($[M + H]^+$) m/z 276.1236, found m/z 276.1232.

2-Ethyl-4,6-dimethylisoindoline-1,3-dione (35). Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and ethyl isocyanate (0.059 mL, 53.3 mg, 0.75 mmol) provide imide **35** as a white solid (81 mg, 0.4 mmol, 80%), R_f = 0.50 (90:10 hexanes/ethyl

acetate), mp 62 – 64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.20 (s, 1H), 3.67 (q, *J* = 7.2 Hz, 2H), 2.61 (s, 3H), 2.41 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 169.0, 168.4, 144.4, 137.5, 136.6, 133.0, 126.4, 121.4, 32.5, 21.7, 17.4, 13.9. HRMS (ESI): Calcd. for $C_{12}H_{14}NO_2$ ($[M + H]^+$) m/z 204.1024, found m/z 204.1020.

2-Benzyl-4,6-dimethylisoindoline-1,3-dione (36). Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and benzyl isocyanate (0.093 mL, 99.9 mg, 0.75 mmol) provide imide **36** as a white solid (81 mg, 0.32 mmol, 63%), R_f = 0.35 (90:10 hexanes/ethyl acetate), mp 126 - 128 °C.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.22 (s, 1H), 4.07 (tt, *J* = 12.3, 3.9 Hz, 1H), 2.63 (s, 3H), 2.43 (s, 3H), 2.20 (qd, *J* = 12.5, 3.4 Hz, 2H), 1.89 – 1.82 (m, 2H), 1.74 – 1.65 (m, 3H), 1.41 – 1.24 (m, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 169.3, 168.6, 144.2, 137.4, 136.6, 132.9, 126.2, 121.3, 50.6, 29.9, 26.1, 25.2, 21.7, 17.3. HRMS (ESI): Calcd. for $C_{16}H_{20}NO_2$ ($[M + H]^+$) m/z 258.1494, found m/z 258.1489.

2-Cyclohexyl-4,6-dimethylisoindoline-1,3-dione (37). Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and cyclohexyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **37** as a white solid (81 mg, 0.32 mmol, 63%), R_f = 0.35 (90:10 hexanes/ethyl acetate), mp 126 - 128 °C.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.22 (s, 1H), 4.07 (tt, *J* = 12.3, 3.9 Hz, 1H), 2.63 (s, 3H), 2.43 (s, 3H), 2.20 (qd, *J* = 12.5, 3.4 Hz, 2H), 1.89 – 1.82 (m, 2H), 1.74 – 1.65 (m, 3H), 1.41 – 1.24 (m, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 169.3, 168.6, 144.2, 137.4, 136.6, 132.9, 126.2, 121.3, 50.6, 29.9, 26.1, 25.2, 21.7, 17.3. HRMS (ESI): Calcd. for $C_{16}H_{20}NO_2$ ($[M + H]^+$) m/z 258.1494, found m/z 258.1489.

2-Dodecyl-4,6-dimethylisoindoline-1,3-dione (38). Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and dodecyl isocyanate (0.181 mL, 159 mg, 0.75 mmol) provide imide **38** is isolated as a light brown oil (65 mg, 0.19 mmol, 38%), R_f = 0.5 (95:5 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.25 (s, 1H), 3.64 (t, *J* = 7.3 Hz, 2H), 2.65 (s, 3H), 2.45 (s, 3H), 1.66 (p, *J* = 7.1 Hz, 2H), 1.38 – 1.21 (m, 18H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.3, 168.7, 144.4, 137.5, 136.6, 133.0, 126.4, 121.4, 37.8, 31.9, 29.62, 29.61, 29.56, 29.49, 29.33, 29.21, 28.63, 26.9, 22.7, 21.7, 17.4, 14.1. HRMS (ESI): Calcd. for $C_{22}H_{33}NO_2Na$ ([M + Na]$^+$) m/z 366.2409, found m/z 366.2402.

2-Cyclohexyl-4-hydroxy-1H-benzo[f]isoindole-1,3(2H)-dione (39). Using the general procedure, 1-methoxy-2-naphthoic acid (101 mg, 0.5 mmol) and ethyl isocyanate (0.096 mL, 93.9 mg, 0.75 mmol) provide imide **39** as a white solid (50 mg, 0.17 mmol, 34%), R_f = 0.61 (80:20 hexanes/ethyl acetate), mp 154 – 156 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.70 – 7.65 (m, 1H), 4.91 (tt, J = 12.3, 3.7 Hz, 1H), 2.47 (qd, *J* = 12.6, 3.5 Hz, 2H), 1.96 – 1.88 (m, 2H), 1.82 – 1.70 (m, 3H), 1.46 (qt, *J* = 13.1, 3.3 Hz, 2H), 1.32(qt, *J* = 12.9, 3.7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 161.5, 150.7, 147.5, 137.0, 130.1, 128.0, 127.5, 125.0, 122.6, 122.0, 121.8, 109.8, 5.2, 28.5, 26.2, 25.1. HRMS (ESI): Calcd. for $C_{18}H_{17}NO_3Na$ ([M + Na]$^+$) m/z 318.1106, found m/z 318.1102.

3,5-Dimethyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (40). Using the general procedure, 3,5-dimethylbenzoic acid (75 mg, 0.5 mmol) and 3-(trifluoromethyl)phenyl isocyanate (0.103 mL,

140 mg, 0.75 mmol) provide a mixture of imide **30** and amide **40**. Following chromatographic separation, amide **40** is isolated as a white solid (18 mg, 0.06 mmol, 12%), R_f = 0.75 (75:25 hexanes/ethyl acetate), mp 134 - 136°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 – 7.91 (m, 3H), 7.54 – 7.47 (m, 3H), 7.45 – 7.40 (m, 1H), 7.23 (s, 1H). 2.41 (s, 6H). ^{3}C NMR (125 MHz, $CDCl_3$): δ 166.2, 138.7, 138.6, 134.4, 133.8, 131.5 (q, *J* = 32.3 Hz), 129.6, 124.8, 123.8 (q, *J* = 273.8 Hz), 120.9 (q, *J* = 3.5 Hz), 116.7 (q, *J* = 3.8 Hz). HRMS (ESI): Calcd. for $C_{16}H_{15}F_3NO$ ($[M + H]^+$) m/z 294.1105, found m/z 294.1101.

Isoquinoline-1,3(2H,4H)-dione (43).[18] Using a modified general procedure (triflic acid is added and allowed to react for 5 minutes before quenching), phenylacetic acid (68.1 mg, 0.5 mmol) and (trimethylsilyl)isocyanate (0.102 mL, 86.4 mg, 0.75 mmol) provide compound **43** as a white solid (40 mg, 0.25 mmol, 50%). ^{1}H NMR (300 MHz, DMSO-d6): δ 11.28 (s, 1H), 8.02 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.63 (ddd, *J* = 7.6, 7.5, 1.3 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 4.03 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6): δ 171.4, 165.8, 137.1, 133.9, 128.3, 127.9, 127.6, 125.5, 36.4. HRMS (ESI): Calcd. for $C_9H_8NO_2$ ($[M + H]^+$) m/z 162.0555, found m/z 162.0556.

Associated Content

Supporting Information. ^{1}H and ^{13}C NMR spectra of prepared compound. Available free of charge on the ACS Publication website at DOI:

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Notes

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