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Formation of Synthetically Versatile 2-Aminobenzophenones from Readily Accessed Acyl Hydrazides

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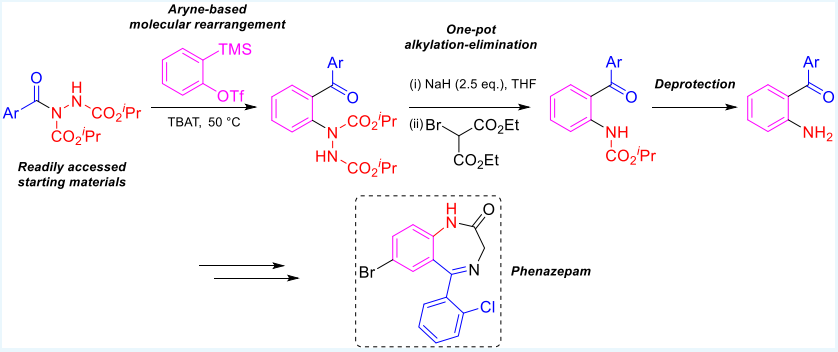
Supporting Information



ABSTRACT: Herein, we report the transformation of readily accessed acyl hydrazides into protected 2-aminobenzophenones via a two-step process involving an aryne-based molecular rearrangement followed by a one-pot addition−elimination procedure. The assembly of the scaffold is tolerant of a wide variety of functional groups, and the carbamate group on the product can be facilely removed to afford highly valuable 2-aminobenzophenones. Application of the protocol was demonstrated in the synthesis of neurological medicine phenazepam.

INTRODUCTION

2-Aminobenzophenones are a very important class of compounds in medicinal and organic chemistry. Compounds bearing this structure have displayed desirable pharmacological use as antimitotic,[1] antitumor,[2] and antiproliferative[3] agents, as well as skeletal muscle relaxants.[4] 2-Aminobenzophenones are also useful starting materials for the synthesis of a wide variety of fine chemicals such as acridones,[5] quinolines,[6−8] quinazolines,[9−11] quinolinones,[12] quinoxalinones,[13] fluorenones,[14] benzisoxazoles,[15] indazoles,[16] indoles,[17] 2-quinazolinones,[18] benzothiophenes,[19] diaryldibenzodiazocines,[20] and (perhaps most noteworthy) benzodiazepines.[21−24] As such, various methodologies for the synthesis of 2-aminobenzophenones and their derivatives have been developed, including (i) Friedel−Crafts acylation of para-substituted anilines;[25,26] (ii) reaction of 2-aminobenzaldehydes with aryl Grignard reagents followed by oxidation with $CuCl_2$;[27] (iii) Pd-catalyzed addition of arylboronic acids[28] or sodium arylsulfinates[29] to 2-aminobenzonitriles; (iv) Pd-catalyzed C−H bond coupling of ortho-directed anilines;[30] and (v) aryl insertion into the C−N of amides[31] or imides.[32] Unfortunately, however, many of these processes suffer from either poor substrate scope (e.g., Friedel−Crafts processes falter when utilizing electron-poor arenes), require multiple reaction steps (e.g., the Grignard-based route obviates the presence of acidic protons and requires product oxidation to obtain the ketone), or require the use of expensive metal catalysts (e.g., $Pd(OAc)_2$, $Pd(TFA)_2$). Application of aryne insertion chemistry appears to be the most promising of these conditions; however, work here has been primarily focused on the formation of *N*-aryl 2-aminobenzophenones.[31]

There has been a substantial number of recent reports for the synthesis of acyl hydrazides and their conversion into a variety of useful chemical functionalities.[33] More specifically, facilely accessed acyl hydrazides have been reported as shelf-stable intermediates for the creation of esters, thioesters, amides,[34] ketones,[35] *N*-acyl carbamates,[36] 1*H*- and 2*H*-indazoles,[37] and 1,3,4-oxadiazoles,[38] as well as being employed as precursors for the formation of bioactive molecules such as hydroxamic acids[39] and macrocyclic enamides.[40] Recently, we developed conditions for the reaction of arynes with acyl hydrazides in which a novel molecular rearrangement reaction pathway facilitates the formation of 2-hydrazobenzophenones.[37] We envisioned that the transformation of this entity into useful 2-aminobenzophenones would be possible via rupture of the N−N bond in a one-pot alkylation−E1cB elimination procedure (Scheme 1). The cleavage of the N−N bond without the use of hydrogenation procedures involving expensive/undesirable metals was seen as a key aspect in itself; this is particularly well described in related work by Magnus et al.[41] Finally, we postulated that our methodology could be applied for the synthesis of medicinally relevant benzodiazepines.

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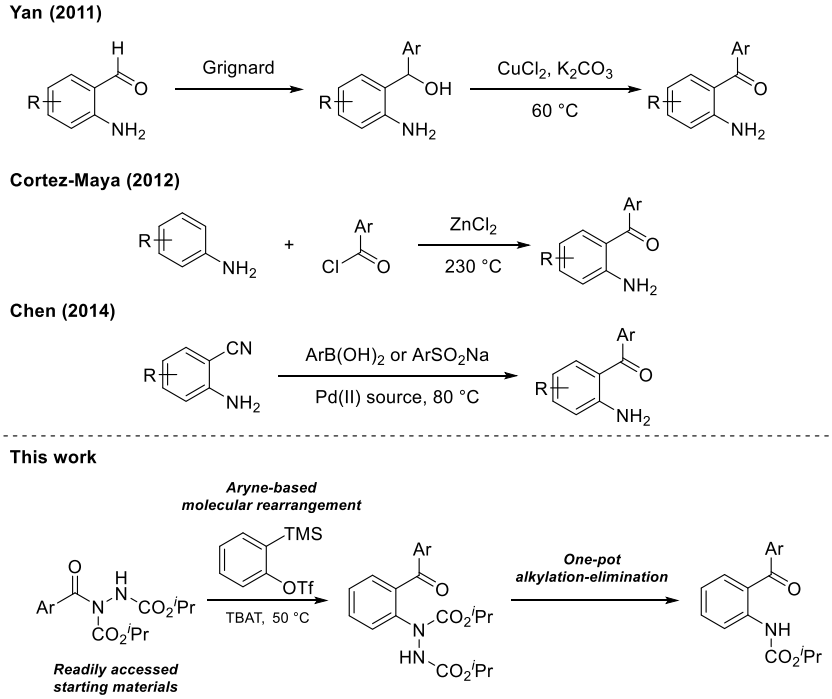
Scheme 1. Synthetic Routes To Access 2-Aminobenzophenones



RESULTS AND DISCUSSION

Our study began with the reaction of 2-hydrazobenzophenone **1a** with *tert*-butyl bromoacetate **2a** in the presence of a base with the aim of forming protected 2-aminobenzophenone **3a** in a two-step one-pot procedure. Initially, the reaction was carried out using an excess of NaH at 20 °C (Table 1, entry 1).[36] While these conditions did provide access to desired product **3a**, it was only in a modest yield of 45%. Increasing the temperature to 50 °C had a positive effect on yield with 67% of **3a** being isolated (Table 1, entry 2).

Table 1. Reaction Optimization for the Formation of Protected 2-Aminobenzophenone 3a

entry	base	equiv	T (°C)	alkylating agent	equiv	yield **3a**[a] (%)	yield **4** (%)
1	NaH	5	20	**2a**	1.1	45 (72)	0
2	NaH	5	50	**2a**	1.1	67	0
3	NaH	3	50	**2a**	1.1	60	12
4[b]	NaH	1 + 1	20	**2a**	1.1	77	0
5[c]	NaH	1	20	**2b**	1.1	35 (55)	0
6[d]	NaH	2	20	**2b**	2	57	10
7[d]	NaH	2.5	20	**2b**	2.5	53	0
8[e]	NaH	2.5	20	**2b**	2.5	82	0
9	Cs_2CO_3	2.5	20	**2b**	2.5	20 (90)	19
10	NEt_3	2.5	20	**2b**	2.5	0 (2)	0
11	NaO^{t}Bu	2.5	20	**2b**	2.5	23 (44)	0
12	NaOEt	2.5	20	**2b**	2.5	42 (77)	0

[a]Conversion of starting material **1a** given in parentheses when not 100%. [b]Stepwise procedure with intermediate **4a** isolated. [c]45% of starting material recovered. [d]Malonate salt observed. [e]Dropwise addition of alkylating agent.

Unfortunately, the efficiency of the reaction was not improved by lowering the number of equivalents of base to 3, where a 60% yield of the desired product and a 12% yield of alkylated-hydrazide intermediate **4a** were recovered (Table 1, entry 3). We next decided to try a two-step process, i.e., the use of 1 equiv of NaH and 1.1 equiv of *tert*-butyl bromoacetate **2a** at room temperature to isolate the resulting alkylated acyl hydrazide intermediate **4a** and then subjecting this intermediate to an additional equivalent of NaH relative to intermediate isolated. This resulted in an improved overall isolated yield, 77%, of desired product **3a** over the two steps (Table 1, entry 4). In an effort to further improve the efficiency of the process, we utilized an alkylating agent with two electron-withdrawing groups in an attempt to promote elimination. We first utilized 1.1 equiv of diethyl bromomalonate **2b** as the alkylating agent with 1 equiv of NaH in an attempt to isolate alkylated intermediate **4b** (Table 1, entry 5). Interestingly, no intermediate was isolated under these conditions with a 35% yield of the protected 2-amino-benzophenone product **3a** and 45% recovery of starting material **1a** observed. We suspected that the increased acidity of the α proton in alkylated-hydrazide intermediate **4b** resulted in rapid elimination to product **3a**. In an attempt to exploit this, a one-pot procedure using 2 equiv of base and alkylating agent was trialed; however, this resulted in only a 57% yield of **3a** due to the formation of a significant amount of a malonate salt (Table 1, entry 6). Increasing the equivalents of NaH and malonate **2b** to 2.5 resulted in a slight decrease in yield (53%) with even more malonate salt observed (Table 1, entry 7). We therefore added malonate **2b** dropwise to minimize the consumption of NaH prior to intermediate **4b** formation. Gratifyingly, this resulted in a high yield of the desired product, 82% (Table 1, entry 8), with no intermediate or malonate salt observed. Having established a procedure that led to the formation of **3a** in excellent yield, the suitability of other bases was appraised (Table 1, entries 9−12). Unfortunately, the substitution of NaH for weaker bases (i.e., Cs_2CO_3, NEt_3, NaO^{t}Bu, NaOEt) proved detrimental to yield with triethylamine not even facilitating the initial alkylation step. The other bases were able to carry out the alkylation and E1cB elimination steps, but gave low yields of the desired product. In the case of using Cs_2CO_3, we highlight that although

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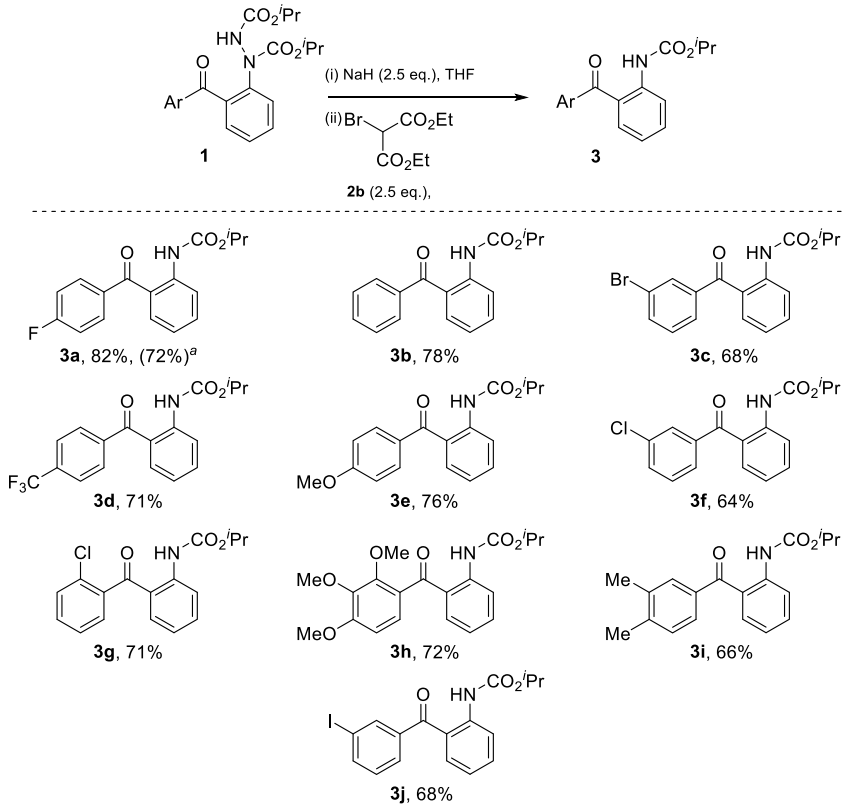
Scheme 2. Reaction Scope for the Formation of Protected 2-Aminobenzophenones 3[b]



[a]Gram scale. [b]Reaction conditions: 2-aminobenzophenone **1** (0.50 mmol, 1 equiv) with NaH (1.25 mmol, 2.5 equiv) in tetrahydrofuran (THF) (3 mL) followed by the dropwise addition of diethyl bromomalonate **2b** (1.25 mmol, 2.50 equiv) at 20 °C for 4 h.

compounds **3a** and **4b** were isolated, the crude reaction mixture appeared to be a complex mixture of many products.

With the optimized conditions for the transformation of 2-hydrazobenzophenones into protected 2-aminobenzophenones in hand, we took the opportunity to investigate the applicability of our protocol for the formation of various protected 2-aminobenzophenones (Scheme 2). A range of 2-hydrazobenzophenones were examined (**1a**−**1j**) under the developed reaction conditions. All of the starting 2-hydrazobenzophenones were prepared in good yields using our previously reported procedure for the reaction of acyl hydrazides with benzynes (see the Supporting Information for details).

To our delight, the reaction was tolerant of various functional groups on the aromatic motif (e.g., halo, methyl, methoxy, and trifluoromethyl functionalities) with good to excellent yields (64−82%) observed. The reaction protocol proved to be tolerant of electron-poor, electron-neutral, and electron-rich aromatic rings, with ortho-, meta-, and para-substitutions having no significant effect on yield. The optimized protocol was also shown to be applicable to a gram-scale synthesis, with compound **3a** being prepared in a 72% yield.

Having established an efficient protocol for the formation of protected 2-aminobenzophenones, we next investigated conditions for deprotection. Initially, we trialed previously reported Brønsted-acid-based conditions[42] and observed that refluxing **3b** in HCl (12 M) resulted in the full conversion of starting material with an excellent yield of 2-aminobenzophenone **5b** obtained (Table 2, entries 1 and 2). Other previously reported conditions, the use of aqueous KOH in dimethylacetamide,[43] did not result in the full conversion of starting material; even

Table 2. Reaction Optimization for the Formation of 2-Aminobenzophenone 5b[a]

entry	reagent	solvent	T (°C)	conversion **3b** (%)	yield **5b** (%)
1	HCl (12 M)	dioxane	110	100	88
2	HCl (12 M)	EtOAc	110	100	83
3	KOH (0.3 M)	DMA	60	26	22
4	KOH (0.5 M)	DMA	60	42	30
5	KOH (1 M)	DMA	110	51	38
6	KOH (4 M)	DMA	110	67	59
7	KOH (8 M)	DMA	110	56	54
8	$AlCl_3$ (4 equiv)	DCM	0 (45 min)	100	92

[a]DMA = *N*,*N*-dimethylacetamide. DCM = dichloromethane. All reactions carried out over 16 h unless stated otherwise in parentheses.

increasing the reaction temperature and concentration of KOH did not improve the yield and conversion significantly (Table 2, entries 3−7). Most pleasingly, however, the use of Lewis acid $AlCl_3$ in dichloromethane resulted in the rapid deprotection (45 min) of the isopropyl carbamate with an exceptional isolated yield of product **5b** observed, 92% (Table 2, entry 8; a 60% overall yield of **5b** from its corresponding acyl hydrazide).[44] The assertion of Lewis acidity having a role in the reaction is based on the fact that the use of HCl (12 M) alone (in either 1,4-dioxane or EtOAc) only resulted in complete conversion after 16 h at 110 °C, i.e., rather than being complete in 45 min at 0 °C when using $AlCl_3$. In fact, the reaction when using HCl (12 M) after 16 h at room temperature only resulted in an 11% yield of **5b** (17% conversion of **3b**). The optimized deprotection conditions were

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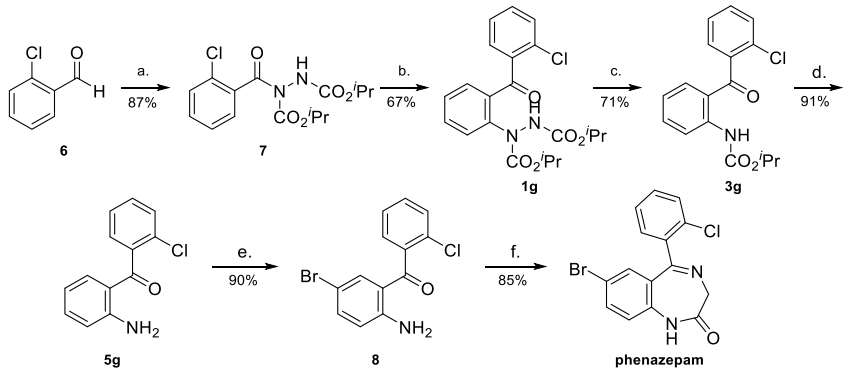
Scheme 3. Synthesis of Phenazepam[a]



[a]Reagents and conditions: (a) DIAD (1.1 equiv), H_2O, rt, 24 h; (b) 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (1.5 equiv), TBAT (2 equiv), toluene, 60 °C, 16 h; (c) NaH (2.5 equiv), THF, diethyl bromomalonate (2.5 equiv, dropwise addition), rt, 4 h; (d) $AlCl_3$ (4 equiv), DCM, rt, 45 min; (e) NBS (1 equiv), DCM, 0 °C, 1 h; (f) bromoacetyl bromide (1.1 equiv), DCM, 0 °C, 1 h, followed by NH_3, EtOH, rt, 24 h. TBAT = tetrabutylammonium difluorotriphenylsilicate.

then trialed on electron-poor and electron-rich protected 2-aminobenzophenones **3d** and **3h** (respectively). To our delight, this afforded the corresponding 2-aminobenzophenones **5d** and **5h** in excellent yields (>85%, Table 2, inset).

Recognizing the potential of the protocol for the synthesis of functional 2-aminobenzophenones, we turned our attention to providing a tangible application of the protocol for the synthesis of a pharmaceutically relevant benzodiazepine (Scheme 3), as a representative example, especially as aryne chemistry is being increasingly employed to synthesize such systems.[45] Phenazepam is a member of a class of molecules that have found use in the treatment of various psychiatric and neurological disorders.[46] Furthermore, phenazepam can be employed as a precursor for the formation of more complex benzodiazepines such as cinazepam and 3-hydroxyphenazepam.[47] We envisioned that phenazepam could be readily accessed via our optimized methodology. More specifically, the chloro entity could be incorporated through the use of starting aldehyde **6** and the bromo substituent could be installed through para-directed bromination of 2-aminobenzophenone **8**. Initially, 2-chlorobenzaldehyde **6** was transformed into the corresponding acyl hydrazide **7** via hydroacylation of diisopropyl azodicarboxylate (DIAD). Aryl insertion into the C(O)−N bond utilizing aryne-based molecular transformation resulted in 2-hydrazobenzophenone **1g** in a 67% yield. This species was submitted to our addition−elimination protocol to afford protected 2-aminobenzophenone **3g** in a 71% yield. Lewis acidic deprotection of the carbamate group afforded 2-aminobenzophenone **5g** in a 91% yield. para-Directed electrophilic bromination using NBS introduced bromine at the 7-position to form **8** in a 90% yield. Finally, a one-pot alkylation−cyclization procedure led to an excellent yield of phenazepam (85%). As such, through the application of our novel methodology, we were able to obtain the desired benzodiazepine in good yield (and even without any of the reaction steps being optimized).

CONCLUSIONS

In conclusion, we have shown 2-hydrazobenzophenones to be excellent candidates for the synthesis of functional 2-aminobenzophenones, which have many applications in terms of their pharmacological and synthetic uses (as exemplified by the extensive catalogue of bioactive molecules they can be transformed into).[5−24] A one-pot, alkylation−E1cB elimination procedure to produce isopropyl carbamate protected 2-aminobenzophenones from 2-hydrazobenzophenones has been developed. Moreover, the protocol is tolerant of many functional groups, and the deprotection of the isopropyl carbamate has been optimized to produce 2-aminobenzophenones in high yield. Finally, the application of both of these methods was demonstrated in the synthesis of phenazepam.

EXPERIMENTAL SECTION

General Experimental Methods. All reagents were purchased from Sigma-Aldrich or AlfaAesar and were used as received without further purification unless otherwise stated. Where described below, petrol refers to petroleum ether (b.p. 40−60 °C). All reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel plates. Silica get plates were initially examined under short-wave UV light and then developed with the use of an aqueous potassium permanganate stain. Flash column chromatography was carried out with preloaded GraceResolv flash cartridges on a Biotage Isolera Spektra One flash chromatography system. Quoted yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^{1}H NMR spectra were recorded at 300, 600, or 700 MHz and ^{13}C NMR at 150 or 175 MHz on a Bruker Avance 300, Bruker Avance III 600, or Bruker Avance Neo 700 spectrometer. All spectra were recorded at room temperature unless stated otherwise. The chemical shifts (δ) for ^{1}H and ^{13}C are quoted relative to residual signals of the solvent on the parts per million (ppm) scale. Coupling constants (J values) are reported in hertz (Hz) and are reported as J_{H-H} unless otherwise stated. Signal multiplicities in ^{13}C NMR were determined using the distortionless enhancement by polarization transfer (DEPT) spectral editing technique. Melting points were measured with a Gallenkamp apparatus and are uncorrected.

General Experimental for the Formation of Acyl Hydrazides: Method A. To a solution of azodicarboxylate (6.00 mmol, 1.2 equiv) in H_2O (1 mL) was added aldehyde (5.00 mmol, 1.0 equiv), and the reaction mixture was stirred at 21 °C for 48 h. The resulting solution was extracted with EtOAc (3 × 15 mL). The combined extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated in vacuo. The resultant crude residue was purified as described below.

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Diisopropyl 1-(4-Fluorobenzoyl)hydrazine-1,2-dicarboxylate. Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(4-fluorobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (1.21 g, 3.70 mmol, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80−7.62 (m, 2H), 7.11 (t, J = 8.5 Hz, 2H), 6.95−6.70 (m, NH, 1H), 5.02 (septet, J = 6.1 Hz, 1H), 4.92 (septet, J = 6.1 Hz, 1H), 1.30 (d, J = 5.2 Hz, 6H), 1.12 (d, J = 5.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3 (C), 165.2 (d, J_{C-F} = 253.4 Hz, C), 155.4 (C), 152.9 (C), 131.3 (d, J_{C-F} = 2.7 Hz, CH), 131.1 (d, J_{C-F} = 9.8 Hz, CH), 115.5 (d, J_{C-F} = 22.1 Hz, CH), 72.8 (CH), 70.9 (CH), 22.0 (CH_3), 21.5 (CH_3); IR (solid) 3306, 2984, 2939, 1704, 1602, 1507 cm^{-1}.

Diisopropyl 1-Benzoylhydrazine-1,2-dicarboxylate. Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-benzoylhydrazine-1,2-dicarboxylate as a white solid (1.02 g, 3.30 mmol, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72−7.58 (m, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.15−6.99 (m, NH, 1H), 5.00 (septet, J = 6.3 Hz, 1H), 4.87 (septet, J = 5.9 Hz, 1H), 1.28 (d, J = 5.5 Hz, 6H), 1.04 (d, J = 4.7 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4 (C), 155.5 (C), 153.0 (C), 135.3 (CH), 132.0 (CH), 128.2 (CH), 72.6 (CH), 70.7 (CH), 22.0 (CH_3), 21.4 (CH_3); IR (solid) 3308, 2983, 2938, 1705, 1601 cm^{-1}.

Diisopropyl 1-(3-Bromobenzoyl)hydrazine-1,2-dicarboxylate. Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(3-bromobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (1.20 g, 3.10 mmol, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84−7.73 (m, 1H), 7.67−7.52 (m, 2H), 7.30 (t, J = 7.8 Hz, 1H), 6.99−6.80 (m, NH, 1H), 5.01 (septet, J = 6.0 Hz, 1H), 4.91 (septet, J = 6.0 Hz, 1H), 1.30 (d, J = 5.8 Hz, 6H), 1.10 (d, J = 5.1 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8 (C), 155.3 (C), 152.6 (C), 137.2 (C), 134.8 (CH), 131.0 (CH), 129.9 (CH), 126.7 (CH), 122.2 (C), 73.0 (CH), 71.0 (CH), 22.0 (CH_3), 21.5 (CH_3); IR (solid) 3303, 2983, 2938, 1707, 1568 cm^{-1}.

Diisopropyl 1-(4-(Trifluoromethyl)benzoyl)hydrazine-1,2-dicarboxylate. Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(4-(trifluoromethyl)benzoyl)-hydrazine-1,2-dicarboxylate as a white solid (1.17 g, 3.10 mmol, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82−7.74 (m, 2H), 7.73−7.67 (m, 2H), 6.95−6.70 (m, NH, 1H), 5.03 (septet, J = 6.1 Hz, 1H), 4.91 (septet, J = 6.1 Hz, 1H), 1.31 (d, J = 5.8 Hz, 6H), 1.10 (d, J = 5.1 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2 (C), 155.3 (C), 152.6 (C), 138.8 (C), 133.4 (q, J_{C-F} = 31.9 Hz, C), 128.3 (CH), 125.3 (q, J_{C-F} = 3.0 Hz, CH), 123.7 (q, J_{C-F} = 272.6 Hz, C), 73.1 (CH), 71.1 (CH), 22.0 (CH_3), 21.5 (CH_3); IR (solid) 3308, 2985, 2941, 1709, 1619, 1514 cm^{-1}.

Diisopropyl 1-(4-Methoxybenzoyl)hydrazine-1,2-dicarboxylate. Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(4-methoxybenzoyl)hydrazine-1,2-dicarboxylate as a white solid (1.03 g, 3.05 mmol, 61%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76−7.62 (m, 2H), 6.98−6.64 (m, 3H), 5.00 (septet, J = 6.2 Hz, 1H), 4.92 (septet, J = 6.2 Hz, 1H), 3.86 (s, 3H), 1.29 (d, J = 4.5 Hz, 6H), 1.13 (d, J = 4.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8 (C), 163.1 (C), 155.5 (C), 153.3 (C), 131.2 (CH), 127.0 (C), 113.5 (CH), 72.4 (CH), 70.7 (CH), 55.6 (CH_3), 22.1 (CH_3), 21.6 (CH_3); IR (solid) 3310, 2982, 2938, 1733, 1699, 1604, 1510 cm^{-1}.

Diisopropyl 1-(3-Chlorobenzoyl)hydrazine-1,2-dicarboxylate. Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(3-chlorobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (1.35 g, 3.95 mmol, 79%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.76−7.50 (m, 2H), 7.48 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 6.96−6.75 (m, NH, 1H), 5.01 (septet, J = 6.2 Hz, 1H), 4.91 (septet, J = 5.6 Hz, 1H), 1.29 (d, J = 5.8 Hz, 6H), 1.14−1.08 (m, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.0 (C), 155.3 (C), 152.7 (C), 137.0 (C), 134.4 (CH), 131.9 (CH), 129.6 (CH), 128.2 (CH), 126.3 (C), 73.0 (CH), 71.0 (CH), 22.0 (CH_3), 21.5 (CH_3); IR (solid) 3287, 2981, 2940, 2921, 1710, 1560 cm^{-1}.

Diisopropyl 1-(2-Chlorobenzoyl)hydrazine-1,2-dicarboxylate **7.** Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-chlorobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (1.49 g, 4.35 mmol, 87%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.50−7.42 (m, 1H), 7.41−7.36 (m, 2H), 7.31 (ddd, J = 7.5, 6.8, 1.9 Hz, 1H), 6.82−6.55 (m, NH, 1H), 5.01 (septet, J = 6.1 Hz, 1H), 4.93−4.89 (m, 1H), 1.29 (d, J = 6.1 Hz, 6H), 1.12−1.04 (m, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.7 (C), 155.1 (C), 151.8 (C), 136.3 (C), 131.0 (CH), 130.4 (C), 129.5 (CH), 128.1 (CH), 126.8 (CH), 72.9 (CH), 70.9 (CH), 22.0 (CH_3), 21.4 (CH_3), IR (solid) 3298, 2979, 2944, 2855, 1739, 1710, 1613, 1572 cm^{-1}.

Diisopropyl 1-(2,3,4-Trimethoxybenzoyl)hydrazine-1,2-dicarboxylate. Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2,3,4-trimethoxybenzoyl)-hydrazine-1,2-dicarboxylate as a white solid (797 mg, 2.00 mmol, 40%). Mp 110−112 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25−7.08 (m, 1H), 6.88 (s, NH, 1H), 6.69 (d, J = 8.7 Hz, 1H), 5.00−4.88 (m, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 1.26 (d, J = 5.8 Hz, 6H), 1.20−1.12 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0 (C), 156.4 (C), 155.1 (C), 152.5 (C), 151.4 (C), 141.7 (C), 124.3 (CH), 122.9 (C), 107.0 (CH), 72.3 (CH), 70.5 (CH), 62.1 (CH_3), 61.1 (CH_3), 56.2 (CH_3), 22.0 (CH_3), 21.6 (CH_3); IR (solid) 3310, 2982, 2940, 1737, 1710, 1596 cm^{-1}; LRMS (ESI) 399 (30, $[M + H]^+$), 195 (100, $[M - C_8H_{15}N_2O_4 + H]^+$); HRMS (ESI) calcd for $C_{18}H_{27}N_2O_8$ $[M + H]^+$ 399.1762; observed 399.1760.

Diisopropyl 1-(3,4-Dimethylbenzoyl)hydrazine-1,2-dicarboxylate. Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(3,4-dimethylbenzoyl)hydrazine-1,2-dicarboxylate as a white solid (891 mg, 2.65 mmol, 53%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.47−7.32 (m, 2H), 7.14 (d, J = 7.8 Hz, 1H), 7.10−7.00 (m, NH, 1H), 4.99 (septet, J = 6.3 Hz, 1H), 4.88 (septet, J = 6.0 Hz, 1H), 2.28 (s, 3H), 2.26 (s, 3H), 1.30−1.23 (m, 6H), 1.15−1.04 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4 (C), 155.5 (C), 153.3 (C), 141.5 (C), 136.6 (C), 132.6 (C), 129.6 (CH), 129.4 (CH), 126.2 (CH), 72.3 (CH), 70.6 (CH), 22.0 (CH_3), 21.5 (CH_3), 20.1 (CH_3), 19.7 (CH_3); IR (thin film) 3278, 3010, 2986, 1713, 1531, cm^{-1}; LRMS (ESI) 337 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{15}H_{20}N_3O_7$ $[M + H]^+$ 337.3959, observed 337.3961.

Diisopropyl 1-(3-Iodobenzoyl)hydrazine-1,2-dicarboxylate. Compound prepared according to method A. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(3-iodobenzoyl)hydrazine-1,2-dicarboxylate as a

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white solid (1.11 g, 2.55 mmol, 51%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.01−7.90 (m, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.71−7.53 (m, 1H), 7.16 (t, J = 7.8 Hz, 1H), 5.01 (septet, J = 6.2 Hz, 1H), 4.92 (septet, J = 6.1 Hz, 1H), 1.30 (d, J = 5.9 Hz, 6H), 1.13−1.08 (m, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.6 (C), 155.3 (C), 152.6 (C), 140.8 (CH), 136.8 (CH), 129.9 (CH), 127.3 (CH), 93.4 (CH), 73.0 (CH), 71.0 (CH), 22.1 (CH_3), 21.5 (CH_3); IR (solid) 3300, 2975, 2941, 1711, 1535 cm^{-1}.

(2-Bromophenoxy)trimethylsilane. To a solution of 2-bromophenol (603 μL, 5.70 mmol) in THF (10 mL) was added hexamethyldisilazane (1.57 mL, 7.50 mmol). The solution was refluxed for 2 h and then allowed to cool down to room temperature. The solvent was then removed in vacuo to afford (2-bromophenoxy)trimethylsilane as an orange oil (1.24 g, 5.10 mmol, 89%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.9, 1.6 Hz, 1H), 7.18 (td, J = 8.0, 1.6 Hz, 1H), 6.88 (dd, J = 8.0, 1.5 Hz, 1H), 6.85 (td, J = 7.8, 1.5 Hz, 1H), 0.31 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.6 (C), 133.4 (CH), 128.4 (CH), 122.8 (CH), 120.9 (CH), 115.7 (C), −0.5 (CH_3); IR (thin film) 3056, 2986, 1584 cm^{-1}.

2-(Trimethylsilyl)phenyl Trifluoromethanesulfonate. To a solution of (2-bromophenoxy)trimethylsilane (2.00 g, 8.60 mmol) in THF (20 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M, 3.91 mL, 12.2 mmol). The reaction mixture was stirred for 20 min. After this time, to the solution was added dropwise Tf_2O (1.90 mL, 12.2 mmol). The reaction was allowed to warm slowly to room temperature and stirred for a further 30 min. The solution was quenched with $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent removed in vacuo. Purification by column chromatography (10−80% EtOAc/petrol) afforded 2-(trimethylsilyl)phenyl trifluoromethanesulfonate as a yellow oil (1.46 g, 4.90 mmol, 57%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, J = 7.3 Hz, 1H), 7.45 (td, J = 7.8, 1.5 Hz, 1H), 7.36−7.33 (m, 2H), 0.37 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.2 (C), 136.4 (CH), 132.7 (CH), 131.4 (CH), 127.6 (CH), 119.6 (CH), 118.6 (q, J_{C-F} = 319.9 Hz, C), −0.7 (CH_3); IR (thin film) 3054, 2987 cm^{-1}.

General Experimental for the Formation of 2-Hydrazobenzophenones 1a−j: Method B. To a solution of acyl hydrazide (500 μmol, 1.0 equiv) and TBAT (1.00 mmol, 540 mg, 2.0 equiv) in toluene (6 mL) was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (750 μmol, 182 μL, 1.5 equiv). The reaction mixture was stirred at 50 °C for 16 h. The resulting solution was then allowed to cool down to room temperature, and the solvent was evaporated in vacuo. The resultant crude residue was purified as described below. These 2-hydrazobenzophenone compounds exist as rotamers, and this leads to broadness in peaks + additional peaks (the stereodynamics of the N−N bond about hydrazide-type molecules is well known in the literature; see for example: ref 40). As such, we conducted VT NMR experiments on a model compound (i.e., compound **1a**) to prove that the additional peaks for the 2-hydrazobenzophenones at room temperature were indeed very likely to be due to the rotameric nature of these molecules.

Diisopropyl 1-(2-(4-Fluorobenzoyl)phenyl)hydrazine-1,2-dicarboxylate ***1a.*** Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-(4-fluorobenzoyl)phenyl)-hydrazine-1,2-dicarboxylate as a pale yellow oil (173 mg, 430 μmol, 86%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.83−7.81 (m, 2H), 7.77−7.76 (m, 1H), 7.57−7.54 (m, 1H), 7.42−7.35 (m, 2H), 7.12 (t, J = 7.6 Hz, 2H), 7.12 (br s, 1H, NH), 5.00−4.93 (m, 1H), 4.79 (septet, J = 6.1 Hz, 1H), 1.31−1.22 (m, 6H), 1.16−0.90 (m, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.1 (C), 194.5 (C), 166.1 (d, J_{C-F} = 253.8 Hz, C), 165.9 (d, J_{C-F} = 253.7 Hz, C), 156.1 (C), 155.8 (C), 155.0 (C), 154.5 (C), 141.0 (C), 135.4 (C), 133.5 (C), 133.4 (C), 133.1 (CH), 132.4 (CH), 130.1 (CH), 129.8 (CH), 129.4 (CH), 128.9 (CH), 127.7 (CH), 127.4 (CH), 115.7 (d, J_{C-F} = 21.7 Hz), 71.2 (CH), 70.8 (CH), 70.0 (CH), 22.1 (CH_3), 22.0 (CH_3), 21.8 (CH_3); IR (thin film) 3323, 2921, 2834, 1711, 1666, 1622, 1599, 1574 cm^{-1}; LRMS (ESI) 403 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{21}H_{24}FN_2O_5$ $[M + H]^+$ 403.1664; observed 403.1658.

^{1}H NMR (400 MHz, $CDCl_3$, −57 °C) δ 7.88−7.72 (m, 3H), 7.62−7.58 (m, 1H), 7.45−7.35 (m, 3H), 7.20−7.13 (m, 2H), 5.00−4.72 (m, 2H), 1.38−0.75 (m, 12H).

^{1}H NMR (400 MHz, DMSO-d_6, 120 °C) δ 8.84 (br s, 1H), 7.78−7.75 (m, 2H), 7.59 (ddd, J = 8.1, 7.4, 1.6 Hz, 1H), 7.54 (ddd, J = 8.1, 1.2, 0.5 Hz, 1H), 7.39 (ddd, J = 7.6, 7.4, 1.2 Hz, 1H), 7.38 (ddd, J = 7.6, 1.6, 0.5 Hz, 1H), 7.29−7.25 (m, 2H), 4.84 (septet, J = 6.3 Hz, 1H), 4.79 (septet, J = 6.3 Hz, 1H), 1.21 (d, J = 6.3 Hz, 6H), 1.06 (d, J = 6.3 Hz, 6H).

^{13}C NMR (100 MHz, DMSO-d_6, 120 °C) δ 193.0 (C), 165.1 (d, J_{C-F} = 252.1 Hz, C), 155.7 (C), 153.9 (C), 140.4 (C), 134.8 (C), 133.8 (d, J_{C-F} = 2.8 Hz, C), 132.4 (d, J_{C-F} = 9.5 Hz, CH), 131.1 (CH), 129.0 (CH), 126.5 (CH), 126.5 (CH), 115.3 (d, J_{C-F} = 22.2 Hz, CH), 70.2 (CH), 68.9 (CH), 21.7 (CH_3), 21.4 (CH_3).

Diisopropyl 1-(2-Benzoylphenyl)hydrazine-1,2-dicarboxylate ***1b.*** Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-benzoylphenyl)hydrazine-1,2-dicarboxylate as a pale brown oil (161 mg, 420 μmol, 84%). ^{1}H NMR (700 MHz, $CDCl_3$) 7.80−7.49 (m, 5H), 7.46−7.35 (m, 4H), 7.10−6.87 (m, 1H, NH), 5.06−4.92 (m, 1H), 4.92−4.76 (m, 1H), 1.32−1.22 (m, 6H), 1.18−0.92 (m, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 196.7 (C), 196.1 (C), 156.1 (C), 155.8 (C), 154.9 (C), 154.5 (C), 153.0 (C), 141.0 (C), 137.3 (C), 137.1 (C), 135.6 (C), 133.6 (CH), 133.2 (C), 132.3 (CH), 132.0 (CH), 130.4 (CH), 130.3 (CH), 129.7 (CH), 129.5 (CH), 128.5 (CH), 128.3 (CH), 127.6 (CH), 127.4 (CH), 120.8 (CH), 72.6 (CH), 71.2 (CH), 70.8 (CH), 70.0 (CH), 69.9 (CH), 22.1 (CH_3), 22.1 (CH_3), 22.0 (CH_3), 21.7 (CH_3), 21.5 (CH_3); IR (thin film) 3301, 2981, 2937, 1883, 1716, 1659, 1598, 1579 cm^{-1}; LRMS (ESI) 385 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{21}H_{25}N_2O_5$ $[M + H]^+$ 385.1758; observed 385.1755.

Diisopropyl 1-(2-(3-Bromobenzoyl)phenyl)hydrazine-1,2-dicarboxylate ***1c.*** Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-(3-bromobenzoyl)phenyl)-hydrazine-1,2-dicarboxylate as a clear oil (183 mg, 395 μmol, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02−7.82 (m, 1H), 7.77−7.67 (m, 2H), 7.62−7.56 (m, 1H), 7.55−7.10 (m, 4H), 7.08−6.65 (m, NH, 1H), 5.06−4.77 (m, 2H), 3.96−3.93 (m, 3H), 1.31−0.94 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.0 (C), 194.6 (C), 156.2 (C), 155.8 (C), 154.9 (C), 154.5 (C), 142.0 (C), 141.1 (C), 139.1 (C), 136.4 (CH), 136.1 (CH), 134.8 (CH), 133.3 (CH), 132.7 (CH), 130.1 (CH), 128.9 (CH), 128.7 (CH), 127.7 (CH), 127.4 (CH), 126.1 (C), 122.8 (C), 71.3 (CH), 71.0 (CH), 70.1 (CH), 22.2 (CH_3), 22.1 (CH_3), 22.0 (CH_3), 21.8 (CH_3); IR (thin film) 3312, 2980, 2880, 1715, 1660, 1622, 1595, 1575 cm^{-1}; LRMS (ESI) 487 (30, $[M^{81}Br + Na]^+$), 485 (31, $[M^{79}Br + Na]^+$), 465 (100, $[M^{79}Br +$

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H]$^+$), 463 (98, [M^{79}Br + H]$^+$); HRMS (ESI) calcd for $C_{21}H_{24}BrN_2O_5$ [M^{79}Br + H]$^+$ 463.0863; observed 463.0858.

Diisopropyl 1-(2-(4-(Trifluoromethyl)benzoyl)phenyl)-hydrazine-1,2-dicarboxylate ***1d***. Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-(4-(trifluoromethyl)benzoyl)phenyl)hydrazine-1,2-dicarboxylate as a clear oil (161 mg, 355 μmol, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94−7.85 (m, 2H), 7.83−7.63 (m, 3H), 7.62−7.57 (m, 1H), 7.42−7.34 (m, 2H), 7.09−6.84 (m, NH, 1H), 5.03−4.94 (m, 1H), 4.85−4.75 (m, 1H), 1.30−1.23 (m, 6H), 1.18−0.92 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.4 (C), 194.9 (C), 155.9 (C), 154.9 (C), 141.1 (C), 140.2 (C), 134.7 (C), 132.9 (CH), 130.6 (CH), 130.0 (CH), 129.9 (CH), 129.2 (CH), 128.7 (CH), 127.7 (CH), 127.4 (CH), 125.6 (CH), 123.7 (q, J_{C-F} = 272.2 Hz, C), 119.0 (CH), 71.3 (CH), 71.0 (CH), 70.1 (CH), 22.1 (CH_3), 21.9 (CH_3); IR (thin film) 3323, 2921, 2834, 1711, 1666, 1622, 1599, 1574 cm^{-1}; LRMS (ESI) 453 (100, [M + H]$^+$); HRMS (ESI) calcd for $C_{22}H_{24}F_3N_2O_5$ [M + H]$^+$ 453.1632; observed 453.1630.

Diisopropyl 1-(2-(4-Methoxybenzoyl)phenyl)hydrazine-1,2-dicarboxylate ***1e***. Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-(4-methoxybenzoyl)-phenyl)hydrazine-1,2-dicarboxylate as a pale brown oil (151 mg, 365 μmol, 73%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.77−7.57 (m, 3H), 7.57 (t, J = 7.5 Hz, 1H), 7.41−7.35 (m, 2H), 7.17−7.04 (m, 1H, NH), 6.92 (d, J = 8.6 Hz, 1H), 5.02−4.93 (m, 1H), 4.90−4.75 (m, 1H), 3.87−3.82 (m, 3H), 1.31−1.20 (m, 6H), 1.16−0.90 (m, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.4 (C), 194.7 (C), 164.0 (C), 163.9 (C), 163.1 (C), 156.0 (C), 156.1 (C), 155.7 (C), 155.0 (C), 154.6 (C), 140.8 (C), 136.3 (C), 132.9 (C), 131.9 (CH), 131.1 (CH), 131.1 (CH), 129.8 (CH), 129.6 (CH), 128.9 (CH), 127.6 (CH), 127.4 (CH), 120.8 (CH), 113.8 (CH), 113.5 (CH), 72.6 (CH), 72.3 (CH), 70.7 (CH), 70.6 (CH), 69.9 (CH), 55.7 (CH_3), 55.6 (CH_3), 55.6 (CH_3), 22.1 (CH_3), 22.1 (CH_3), 22.0 (CH_3), 21.7 (CH_3), 21.6 (CH_3); IR (thin film) 3302, 2981, 2937, 2842, 1717, 1652, 1597, 1577 cm^{-1}; LRMS (ESI) 437 (30, [M + Na]$^+$), 415 (100, [M + H]$^+$); HRMS (ESI) calcd for $C_{22}H_{27}N_2O_6$ [M + H]$^+$ 415.1864; observed 415.1862.

Diisopropyl 1-(2-(3-Chlorobenzoyl)phenyl)hydrazine-1,2-dicarboxylate ***1f***. Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-(3-chlorobenzoyl)phenyl)-hydrazine-1,2-dicarboxylate as a pale yellow oil (170 mg, 405 μmol, 81%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.80−7.64 (m, 2H), 7.62−7.46 (m, 2H), 7.45−7.34 (m, 3H), 7.34−7.14 (m, 1H), (m, 1H, NH), 5.07−4.80 (m, 2H), 1.30−0.94 (m, 12H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.1 (C), 194.7 (C), 156.2 (C), 156.1 (C), 155.9 (C), 154.9 (C), 154.5 (C), 142.0 (C), 141.0 (C), 138.9 (C), 138.7 (C), 134.8 (C), 133.5 (CH), 133.2 (CH), 132.7 (CH), 130.4 (CH), 130.0 (CH), 129.9 (CH), 129.2 (CH), 128.7 (CH), 128.4 (CH), 127.8 (CH), 127.4 (CH), 126.2 (CH), 120.8 (CH), 71.3 (CH), 71.0 (CH), 70.1 (CH), 22.1 (CH_3), 22.1 (CH_3), 22.0 (CH_3), 22.0 (CH_3), 21.8 (CH_3); IR (thin film) 3305, 2985, 2884, 1718, 1658, 1619, 1599, 1580 cm^{-1}; LRMS (ESI) 443 (8, [M^{37}Cl + Na]$^+$), 441 (25, [M^{35}Cl + Na]$^+$), 421 (30, [M^{37}Cl + H]$^+$), 419 (100, [M^{35}Cl + H]$^+$); HRMS (ESI) calcd for $C_{21}H_{24}ClN_2O_5$ [M^{35}Cl + H]$^+$ 419.1368; observed 419.1367.

Diisopropyl 1-(2-(2-Chlorobenzoyl)phenyl)hydrazine-1,2-dicarboxylate ***1g***. Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-(2-chlorobenzoyl)phenyl)-hydrazine-1,2-dicarboxylate as a clear oil (140 mg, 335 μmol, 67%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78−6.70 (m, 9H), 5.05−4.86 (m, 2H), 1.29−1.04 (m, 12H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.5 (C), 195.1 (C), 156.0 (C), 155.8 (C), 155.1 (C), 154.6 (C), 151.8 (C), 138.2 (C), 136.3 (C), 135.3 (CH), 135.1 (CH), 134.7 (CH), 134.1 (CH), 134.1 (CH), 133.9 (CH), 133.8 (CH), 132.2 (CH), 132.1 (CH), 132.0 (CH), 131.9 (CH), 131.0 (CH), 130.8 (CH), 130.7 (CH), 130.6 (CH), 130.5 (CH), 130.4 (CH), 129.9 (CH), 129.5 (CH), 128.2 (CH), 128.1 (CH), 120.8 (CH), 127.8 (CH), 126.8 (CH), 72.8 (CH), 71.1 (CH), 70.9 (CH), 70.1 (CH), 69.9 (CH), 69.8 (CH), 22.1 (CH_3), 22.0 (CH_3), 22.0 (CH_3), 21.4 (CH_3); IR (thin film) 3308, 2992, 2888, 1723, 1653, 1617, 1606 cm^{-1}; LRMS (ESI) 443 (9, [M^{37}Cl + Na]$^+$), 441 (26, [M^{35}Cl + Na]$^+$), 421 (31, [M^{37}Cl + H]$^+$), 419 (100, [M^{35}Cl + H]$^+$); HRMS (ESI) calcd for $C_{21}H_{24}ClN_2O_5$ [M^{35}Cl + H]$^+$ 419.1368; observed 419.1370.

Diisopropyl 1-(2-(2,3,4-Trimethoxybenzoyl)phenyl)-hydrazine-1,2-dicarboxylate ***1h***. Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-(2,3,4-trimethoxybenzoyl)phenyl)hydrazine-1,2-dicarboxylate as a clear oil (171 mg, 360 μmol, 72%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.70−7.52 (m, 1H), 7.52−7.46 (m, 1H), 7.44−7.27 (m, 3H), 7.18−7.10 (m, 1H), 6.65 (d, J = 8.7 Hz, 1H), 4.94−4.78 (m, 2H), 3.87−3.66 (m, 9H), 1.27−1.03 (m, 12H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.2 (C), 194.9 (C), 157.4 (C), 157.2 (C), 155.9 (C), 155.6 (C), 155.0 (C), 154.6 (C), 153.7 (C), 142.4 (C), 136.9 (C), 132.6 (CH), 132.3 (CH), 130.9 (CH), 130.6 (CH), 130.1 (CH), 129.9 (CH), 127.6 (CH), 127.0 (CH), 126.7 (CH), 126.2 (CH), 106.8 (CH), 106.7 (CH), 70.9 (CH), 70.5 (CH), 69.7 (CH), 69.6 (CH), 62.1 (CH_3), 61.7 (CH_3), 61.7 (CH_3), 61.1 (CH_3), 61.0 (CH_3), 56.2 (CH_3), 24.0 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 22.0 (CH_3), 21.8 (CH_3); IR (thin film) 3300, 2899, 2815, 1720, 1666, 1614, 1598, 1562 cm^{-1}; LRMS (ESI) 475 (100, [M + H]$^+$); HRMS (ESI) calcd for $C_{24}H_{31}N_2O_8$ [M + H]$^+$ 475.2275 observed 475.2280.

Diisopropyl 1-(2-(3,4-Dimethylbenzoyl)phenyl)hydrazine-1,2-dicarboxylate ***1i***. Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-(3,4-dimethylbenzoyl)phenyl)hydrazine-1,2-dicarboxylate as a yellow oil (151 mg, 365 μmol, 73%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76−7.13 (m, 8H), 5.00−4.77 (m, 2H), 2.31−2.26 (m, 6H), 1.30−0.92 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.9 (C), 189.4 (C), 149.4 (C), 149.1 (C), 148.2 (C), 147.9 (C), 146.5 (C), 136.5 (CH), 136.2 (CH), 134.8 (C), 134.2 (CH), 130.2 (CH), 129.3 (CH), 128.3 (CH), 125.8 (CH), 125.3 (CH), 124.6 (CH), 122.9 (CH), 121.8 (CH), 121.6 (CH), 120.8 (CH), 119.4 (CH), 65.6 (CH), 64.3 (CH), 63.9 (CH), 63.2 (CH), 15.3 (CH_3), 14.0 (CH_3), 13.4 (CH_3); IR (thin film) 3329, 2921, 2840, 1711, 1653, 1622, 1591, 1569 cm^{-1}; LRMS (ESI) 413 (100, [M + H]$^+$); HRMS (ESI) calcd for $C_{23}H_{29}N_2O_5$ [M + H]$^+$ 413.2071; observed 413.2068.

Diisopropyl 1-(2-(3-Iodobenzoyl)phenyl)hydrazine-1,2-dicarboxylate ***1j***. Compound prepared according to method B. Purification by column chromatography (10−50% EtOAc/petrol) afforded diisopropyl 1-(2-(3-iodobenzoyl)phenyl)-hydrazine-1,2-dicarboxylate as a clear oil (179 mg, 350 μmol, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20−8.04 (m, 1H), 7.95−7.87 (m, 1H), 7.82−7.67 (m, 2H), 7.60−7.57 (m, 1H),

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7.47−7.30 (m, 3H), 7.22−7.17 (m, 1H), 7.08−6.84 (m, NH, 1H), 5.02−4.79 (m, 2H), 1.39−0.96 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.9 (C), 194.6 (C), 156.2 (C), 156.1 (C), 155.9 (C), 154.9 (C), 154.5 (C), 142.3 (C), 141.9 (C), 141.1 (C), 141.0 (C), 139.2 (CH), 138.7 (CH), 136.7 (CH), 132.7 (CH), 130.2 (CH), 129.8 (CH), 129.5 (CH), 129.2 (CH), 128.7 (CH), 127.7 (CH), 127.4 (CH), 120.8 (CH), 94.2 (C), 93.4 (C), 71.3 (CH), 71.0 (CH), 70.1 (CH), 22.1 (CH_3), 21.1 (CH_3), 21.1 (CH_3), 22.0 (CH_3) 21.8 (CH_3), 21.6 (CH_3), 21.5 (CH_3); IR (thin film) 3310, 2906, 2844, 1711, 1652, 1619, 1597 cm^{-1}; LRMS (ESI) 511 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{21}H_{24}IN_2O_5$ $[M + H]^+$ 511.0725; observed 511.0720.

General Experimental for the Formation of Isopropyl Carbamate Protected 2-Aminobenzophenones 3a−j: Method C. To a stirring solution of sodium hydride (60% mineral oil dispersion, 50 mg, 1.25 mmol, 2.5 equiv) in anhydrous THF (0.5 mL) under an atmosphere of argon was added dropwise a solution of 2-hydrazobenzophenone (0.5 mmol, 1 equiv) predissolved in anhydrous THF (1 mL), and the reaction mixture was stirred for 5 min. After this time, to the reaction mixture was added diethyl bromomalonate (205 μL, 1.25 mmol, 2.5 equiv) predissolved in 1.5 mL anhydrous THF via a syringe pump (over 30 min, 5.7 μL min^{-1}). The reaction mixture was then stirred at 20 °C for 4 h and monitored via TLC till completion and poured over sat. aq. NH_4Cl (10 mL). The resulting solution was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated in vacuo. The resultant residue was purified as described below.

Isopropyl (2-(4-Fluorobenzoyl)phenyl)carbamate ***3a***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded isopropyl (2-(4-fluorobenzoyl)phenyl)carbamate as a yellow oil (123 mg, 0.410 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (br s, NH, 1H), 8.42 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 8.8, 5.4 Hz, 2H), 7.59−7.53 (m, 1H), 7.49 (dd, J = 7.9, 1.5 Hz, 1H), 7.16 (t, J = 8.6 Hz, 2H), 7.03 (t, J = 8.1 Hz, 1H), 5.01 (septet, J = 6.3 Hz, 1H), 1.30 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7 (C), 165.4 (d, J_{C-F} = 254.4 Hz, C), 153.5 (C), 141.1 (C), 135.0 (C), 134.3 (CH), 133.2 (CH), 132.6 (d, J_{C-F} = 9.2 Hz, CH), 123.0 (CH), 121.1 (CH), 120.2 (C), 115.5 (d, J_{C-F} = 21.8 Hz, CH), 68.9 (CH), 22.1 (CH_3); IR (thin film) 3302, 2981, 2935, 1729, 1633, 1580, 1519 cm^{-1}; LRMS (ESI) 302 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{17}H_{16}FNO_3$ $[M + H]^+$ 302.1192; observed 302.1193.

Isopropyl (2-Benzoylphenyl)carbamate ***3b***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded isopropyl (2-benzoylphenyl)carbamate as a colorless oil (110 mg, 0.390 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (br s, NH, 1H), 8.44 (d, J = 8.7 Hz, 1H), 7.70 (dt, J = 8.4, 1.5 Hz, 2H), 7.61−7.43 (m, 5H), 7.04−6.98 (m, 1H), 5.02 (septet, J = 6.3 Hz, 1H), 1.30 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4 (C), 153.6 (C), 141.3 (C), 138.9 (C), 134.3 (CH), 133.7 (CH), 132.5 (CH), 130.0 (CH), 128.4 (CH), 122.9 (C), 121.0 (CH), 120.0 (CH), 68.9 (CH), 22.2 (CH_3); IR (thin film) 3318, 2979, 2934, 1728, 1635, 1580, 1518 cm^{-1}; LRMS (ESI) 284 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{17}H_{18}NO_3$ $[M + H]^+$ 284.1287; observed 284.1286.

Isopropyl (2-(3-Bromobenzoyl)phenyl)carbamate ***3c***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded isopropyl (2-(3-bromobenzoyl)phenyl)carbamate as a brown oil (123 mg, 0.340 mmol, 68%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.11 (br s, NH, 1H), 8.44 (d, J = 7.9 Hz, 1H), 7.83 (t, J = 1.7 Hz, 1H), 7.70 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.60−7.58 (m, 1H), 7.56 (dd, J = 8.6, 7.5, 1.5 Hz, 1H), 7.49 (dd, J = 7.9, 1.5 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.03 (m, 1H), 5.02 (septet, J = 6.3 Hz, 1H), 1.30 (d, J = 6.3 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 197.8 (C), 153.5 (C), 141.5 (C), 140.8 (C), 135.3 (CH), 134.8 (CH), 133.5 (CH), 132.7 (CH), 129.9 (CH), 128.5 (CH), 122.7 (C), 122.3 (C), 121.2 (CH), 120.1 (CH), 69.1 (CH), 22.2 (CH_3); IR (thin film) 3310, 3082, 2977, 2934, 1723, 1633, 1603, 1577, 1560, 1510 cm^{-1}; LRMS (ESI) 364 (100, $[M^{81}Br + H]^+$), 362 (98, $[M^{79}Br + H]^+$); HRMS (ESI) calcd for $C_{17}H_{16}BrNO_3$ $[M^{79}Br + H]^+$ 362.0392; observed 362.0374.

Isopropyl (2-(4-(Trifluoromethyl)benzoyl)phenyl)-carbamate ***3d***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded isopropyl (2-(4-(trifluoromethyl)benzoyl)-phenyl)carbamate as a yellow oil (125 mg, 0.355 mmol, 71%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.25 (br s, NH, 1H), 8.47 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H), 7.57−7.55 (m, 1H), 7.45 (dd, J = 7.9, 1.5 Hz, 1H), 7.01−6.99 (m, 1H), 5.02 (septet, J = 6.3 Hz, 1H), 1.30 (d, J = 6.4 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 198.3 (C), 153.3 (C), 142.4 (C), 141.8 (CH) 135.0 (CH), 133.7 (CH), 133.6 (q, J_{C-F} = 31.0 Hz, C), 125.4 (q, J_{C-F} = 3.7 Hz, CH), 123.8 (q, J_{C-F} = 272.6 Hz, C), 121.9 (CH), 121.2 (CH), 120.1 (CH), 69.1 (CH), 22.2 (CH_3); IR (thin film) 3340, 2969, 2920, 1727, 1628, 1590, 1579 cm^{-1}; LRMS (ESI) 352 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{18}H_{17}F_3NO_3$ $[M + H]^+$ 352.1155; observed 352.1159.

Isopropyl (2-(4-Methoxybenzoyl)phenyl)carbamate ***3e***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded isopropyl (2-(4-methoxybenzoyl)phenyl)carbamate as a red oil (119 mg, 0.380 mmol, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (br s, NH, 1H), 8.38 (d, J = 8.2 Hz, 1H), 7.76−7.68 (m, 2H), 7.56−7.47 (m, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.98−6.91 (m, 2H), 5.00 (septet, J = 6.3 Hz, 1H), 3.88 (s, 3H), 1.28 (d, J = 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7 (C), 163.4 (C), 153.6 (C), 140.6 (C), 133.6 (CH), 132.9 (CH), 132.7 (CH), 131.2 (C), 123.9 (C), 121.1 (CH), 120.2 (CH), 113.7 (CH), 68.8 (CH), 55.6 (CH_3), 22.2 (CH_3); IR (thin film) 3317, 2980, 2935, 2839, 1728, 1628, 1595, 1580 cm^{-1}; LRMS (ESI) 314 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{18}H_{19}NO_4$ $[M + H]^+$ 314.1392; observed 314.1385.

Isopropyl (2-(3-Chlorobenzoyl)phenyl)carbamate ***3f***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded isopropyl (2-(3-chlorobenzoyl)phenyl)carbamate as a yellow oil (102 mg, 0.320 mmol, 64%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.12 (br s, NH, 1H), 8.45 (dd, J = 8.5, 0.7 Hz, 1H), 7.68 (t, J = 1.7 Hz, 1H), 7.61−7.53 (m, 3H), 7.49 (dd, J = 7.9, 1.5 Hz, 1H), 7.44−7.38 (m, 1H), 7.06−6.99 (m, 1H), 5.02 (septet, J = 6.3 Hz, 1H), 1.30 (d, J = 6.3 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 197.9 (C), 153.6 (C), 141.5 (C), 140.6 (C), 134.8 (CH), 134.7 (C), 133.5 (CH), 132.3 (CH), 129.8 (CH), 129.7 (CH), 128.0 (CH), 122.3 (C), 121.2 (CH), 120.1 (CH), 69.1 (CH), 22.2 (CH_3); IR (thin film) 3313, 3022, 2982, 2936, 1729, 1637, 1604, 1580 cm^{-1}; LRMS (ESI) 320 (40, $[M^{37}Cl + H]^+$), 318 (100, $[M^{35}Cl + H]^+$); HRMS (ESI) calcd for $C_{17}H_{16}ClNO_3$ $[M^{35}Cl + H]^+$ 318.0897; observed 318.0893.

Isopropyl (2-(2-Chlorobenzoyl)phenyl)carbamate ***3g***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded

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isopropyl (2-(2-chlorobenzoyl)phenyl)carbamate as a yellow oil (114 mg, 0.36 mmol, 71%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.94 (br s, NH, 1H), 8.57 (d, J = 8.5 Hz, 1H), 7.59−7.54 (m, 1H), 7.48−7.45 (m, 1H), 7.44 (td, J = 7.8, 1.6 Hz, 1H), 7.37 (td, J = 7.4, 1.0 Hz, 1H), 7.32 (ddd, J = 13.7, 7.8, 1.5 Hz, 2H), 6.94 (t, J = 7.6 Hz, 1H), 5.05 (septet, J = 6.3 Hz, 1H), 1.33 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8 (C), 153.6 (C), 142.8 (C), 139.1 (C), 135.9 (CH), 134.8 (CH), 131.1 (CH), 131.0 (C), 130.2 (CH), 128.8 (CH), 126.8 (CH), 121.2 (CH), 121.0 (C), 119.2 (CH), 69.1 (CH), 22.2 (CH_3); IR (thin film) 3320, 3028, 2981, 2936, 1743, 1721, 1635, 1603, 1582 cm^{-1}; LRMS (ESI) 320 (30, $[M^{37}Cl + H]^+$), 318 (100, $[M^{35}Cl + H]^+$); HRMS (ESI) calcd for $C_{17}H_{16}ClNO_3$ $[M^{35}Cl + H]^+$ 318.0897; observed 318.0894.

Isopropyl (2-(2,3,4-Trimethoxybenzoyl)phenyl)carbamate ***3h***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded isopropyl (2-(2,3,4-trimethoxybenzoyl)phenyl)carbamate as a yellow oil (134 mg, 0.36 mmol, 72%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.74 (br s, NH, 1H), 8.46 (d, J = 7.9 Hz, 1H), 7.51−7.47 (m, 1H), 7.43 (dd, J = 8.0, 1.5 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 6.92−6.90 (td, J = 7.4, 1.0 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 5.00 (septet, J = 6.3 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.76 (s, 3H), 1.29 (d, J = 6.3 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 198.8 (C), 156.1 (C), 153.7 (C), 152.3 (C), 142.1 (C), 141.7 (C), 134.8 (CH), 134.3 (CH), 127.1 (C), 124.6 (CH), 123.0 (C), 120.9 (CH), 119.1 (CH), 106.8 (CH), 68.8 (CH), 61.9 (CH), 61.0 (CH), 56.2 (CH), 22.2 (CH_3); IR (thin film) 3301, 3012, 2977, 2929, 1740, 1639, 1593, 1589 cm^{-1}; LRMS (ESI) 374 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{20}H_{23}NO_6$ $[M + H]^+$ 374.1598; observed 374.1601.

Isopropyl (2-(3,4-Dimethylbenzoyl)phenyl)carbamate ***3i***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded isopropyl (2-(3,4-dimethylbenzoyl)phenyl)carbamate as a brown oil (103 mg, 0.330 mmol, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (br s, NH, 1H), 8.40 (m, 1H), 7.53 (m, 3H), 7.43 (dd, J = 7.8, 1.7 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.06−6.99 (m, 1H), 5.00 (septet, J = 6.3 Hz, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 1.29 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2 (C), 153.6 (C), 142.1 (C), 140.9 (C), 136.8 (C), 136.5 (C), 133.8 (CH), 133.4 (CH), 131.2 (CH), 129.5 (CH), 128.0 (CH), 123.5 (C), 120.9 (CH), 120.0 (CH), 68.8 (CH), 22.1 (CH_3), 20.1 (CH_3), 19.8 (CH_3); IR (thin film) 3286, 2978, 2923, 2853, 1730, 1633, 1600, 1580, 1518 cm^{-1}; LRMS (ESI) 312 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{19}H_{21}NO_3$ $[M + H]^+$ 312.1594; observed 312.1596.

Isopropyl (2-(3-Iodobenzoyl)phenyl)carbamate ***3j***. Compound prepared according to method C. Purification by column chromatography (10−50% EtOAc/petrol) yielded isopropyl (2-(2-chlorobenzoyl)phenyl)carbamate as a yellow oil (139 mg, 0.34 mmol, 68%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.11 (br s, NH, 1H), 8.43 (d, J = 8.5 Hz, 1H), 8.01 (t, J = 1.6 Hz, 1H), 7.88 (ddd, J = 7.9, 1.7, 1.1 Hz, 1H), 7.61−7.60 (m, 1H), 7.55 (ddd, J = 8.6, 7.5, 1.4 Hz, 1H), 7.47 (dd, J = 7.9, 1.5 Hz, 1H), 7.19 (t, J = 7.8 Hz, 2H), 7.02−7.00 (m, 1H), 5.01 (septet, J = 6.3 Hz, 1H), 1.29 (d, J = 6.3 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 197.6 (C), 153.5 (C), 141.5 (C), 141.1 (C), 140.8 (CH), 138.5 (CH), 134.8 (CH), 133.5 (C), 130.0 (CH), 129.0 (CH), 122.2 (CH), 121.2 (CH), 120.1 (C), 94.1 (C), 69.0 (CH), 22.2 (CH_3); IR (thin film) 3318, 3025, 2984, 2940, 1737, 1719, 1640, 1603 cm^{-1}; LRMS (ESI) 410 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{17}H_{17}INO_3$ $[M + H]^+$ 410.0248; observed 410.0251.

General Experimental for the Deprotection of Isopropyl Carbamate Protected 2-Aminobenzophenones 5: Method D. To a stirring solution of aluminum chloride (4 mmol, 4 equiv) in dichloromethane (2 mL) was added dropwise isopropyl carbamate protected 2-aminobenzophenone (1 mmol, 1 equiv) predissolved in dichloromethane (0.5 mL). The mixture was then stirred for 1 h and monitored via TLC till completion. The reaction mixture was then poured into ice water (10 mL). If a solid precipitate was formed, the mixture was filtered and the solid was washed with water (3 × 3 mL) and dried in vacuo. If no solid was formed, the mixture was then extracted with EtOAc (3 × 4 mL). The combined organic extracts were then washed with water (3 × 4 mL), dried ($MgSO_4$), and concentrated in vacuo. The resultant residue was purified as described below.

(2-Aminophenyl)(phenyl)methanone ***5b***. Compound prepared according to method D. Purification by column chromotography (10−25% EtOAc/petrol) yielded (2-aminophenyl)(phenyl)methanone as a yellow crystalline solid (180 mg, 0.920 mmol, 92%). Mp 103−104 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.64 (d, J = 7.8 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.1 Hz, 2H), 7.46 (t, J = 7.1 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.60 (t, J = 7.5 Hz, 1H), 6.10 (br s, NH, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 199.2 (C), 151.1 (C), 140.3 (C), 134.7 (CH), 134.4 (CH), 131.2 (CH), 129.3 (CH), 128.2 (CH), 118.3 (C), 117.2 (CH), 115.7 (CH); IR (solid) 3502, 3087, 3056, 3031, 1669, 1593, 1575 cm^{-1}; LRMS (ESI) 198 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{13}H_{11}NO$ $[M + H]^+$ 198.0919; observed 198.0916.

(2-Aminophenyl)(4-(trifluoromethyl)phenyl)methanone ***5d***. Compound prepared according to method D. Purification by column chromotography (10−25% EtOAc/petrol) yielded (2-aminophenyl)(4-(trifluoromethyl)phenyl)methanone as a yellow crystalline solid (236 mg, 0.890 mmol, 89%). Mp 98−99 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.74−7.70 (m, 4H), 7.35 (dd, J = 8.1, 1.3 Hz, 1H), 7.32 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 6.75 (dd, J = 8.4, 1.0 Hz, 1H), 6.60 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 6.21 (br s, NH, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 197.8 (C), 151.4 (C), 143.6 (C), 135.0 (CH), 134.5 (CH), 132.6 (q, J_{C-F} = 32.7 Hz, C), 129.3 (CH), 125.3 (q, J_{C-F} = 3.8 Hz, CH), 123.9 (q, J_{C-F} = 272.4 Hz, CH), 117.4 (C), 117.3 (CH), 115.8 (CH); IR (solid) 3487, 3069, 3040, 3021, 1672, 1590, 1575 cm^{-1}; LRMS (ESI) 266 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{14}H_{11}F_3NO$ $[M + H]^+$ 266.0787; observed 266.0789.

(2-Aminophenyl)(2,3,4-trimethoxyphenyl)methanone ***5h***. Compound prepared according to method D. Purification by column chromatography for (10−25% EtOAc/petrol) yielded (2-aminophenyl)(2,3,4-trimethoxyphenyl)methanone as a yellow crystalline solid (247 mg, 0.860 mmol, 86%). Mp 123−125 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 (dd, J = 8.1, 1.5 Hz, 1H), 7.21 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 6.66 (d, J = 8.3, 0.8 Hz, 1H), 6.51 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 6.35 (br s, NH, 2H), 3.88 (s, 3H), 3.88 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 198.0 (C), 155.1 (C), 151.6 (C), 151.1 (C), 142.1 (C), 134.9 (C), 134.6 (CH), 128.2 (CH), 123.7 (CH), 118.9 (C), 116.9 (CH), 115.5 (CH), 106.9 (CH), 61.8 (CH_3), 61.1 (CH_3), 56.2 (CH_3); IR (solid) 3500, 3084, 3065, 3029, 1670, 1593, 1571 cm^{-1}; LRMS (ESI) 288 (100, $[M + H]^+$); HRMS (ESI) calcd for $C_{16}H_{17}NO_4$ $[M + H]^+$ 288.1231; observed 288.1235.

(2-Aminophenyl)(2-chlorophenyl)methanone ***5g***. Compound prepared according to method D with 0.36 mmol of isopropyl (2-(2-chlorobenzoyl)phenyl)carbamate **3g**. Purifica-

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tion by column chromotography for (10−25% EtOAc/petrol) yielded (2-aminophenyl)(2-chlorophenyl)methanone as a yellow crystalline solid (75 mg, 0.33 mmol, 91%). Mp 57−59 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.47−7.43 (m, 1H), 7.38 (ddd, J = 8.0, 7.3, 1.9 Hz, 1H), 7.34 (td, J = 7.4, 1.2 Hz, 1H), 7.32−7.30 (m, 1H), 7.28 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.17 (dd, J = 8.1, 1.5 Hz, 1H), 6.72 (m, 1H), 6.54 (ddd, J = 8.1, 7.0, 1.1 Hz) 6.47 (br s, NH, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 197.4 (C), 151.6 (C), 140.0 (C), 135.4 (CH), 134.8 (CH), 130.8 (C), 130.5 (CH), 130.0 (CH), 128.6 (CH), 126.8 (CH), 117.5 (C), 117.2 (CH), 115.9 (CH); IR (solid) 3450, 3070, 3041, 3029, 1665, 1591, 1580 cm^{-1}.

(2-Amino-5-bromophenyl)(2-chlorophenyl)methanone ***8***. To a solution of (2-aminophenyl)(2-chlorophenyl)methanone **5g** (75 mg, 0.33 mmol, 1 equiv) in dichloromethane (10 mL) was added *N*-bromosuccinimide (59 mg, 0.33 mmol, 1 equiv) at 0 °C. The mixture was stirred for 1 h at this temperature. After completion of the reaction, the resulting mixture was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted into DCM (3 × 15 mL). The combined organic layers were then dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by column chromotography (10−25% EtOAc/petrol) yielded (2-amino-5-bromophenyl)(2-chlorophenyl)methanone as a yellow crystalline solid (92 mg, 0.30 mmol, 90%). Mp 88−90 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.45 (dd, J = 8.0, 0.7 Hz, 1H), 7.40 (td, J = 7.8, 1.7 Hz, 1H), 7.34 (td, J = 7.5, 1.1 Hz, 1H), 7.32 (d, J = 8.9, 2.3 Hz, 1H), 7.29 (dd, J = 7.5, 1.5 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 6.60 (d, J = 8.9 Hz, 1H), 6.52 (br s, NH, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 196.5 (C), 150.5 (C), 139.1 (C), 138.0 (C), 136.3 (C), 131.0 (C), 130.2 (CH), 128.6 (CH), 127.0 (CH), 119.1 (C), 118.7 (CH), 106.8 (CH); IR (solid) 3350, 3041, 3022, 1627, 1570 cm^{-1}.

Phenazepam. To a solution of (2-amino-5-bromophenyl)-(2-chlorophenyl)methanone **8** (92 mg, 0.30 mmol, 1 equiv) in THF (10 mL) was added bromoacetyl bromide (29 μL, 0.33 mmol, 1.1 equiv) at 0 °C. The mixture was stirred for 1 h at this temperature. After this time, ammonium hydroxide (1.5 mL) in EtOH (2 mL) was added dropwise, and the reaction was allowed to stir for 2 h. After the completion of the reaction, the resulting mixture was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted into EtOAc (3 × 15 mL). The combined organic layers were then dried ($MgSO_4$) and the solvent was removed in vacuo. Purification by column chromatography (0−10% MeOH/DCM) yielded (2-amino-5-bromophenyl)(2-chlorophenyl)-methanone as a yellow crystalline solid (89 mg, 0.260 mmol, 85%). Mp 222−235 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.61 (br s, NH, 1H), 7.57 (dd, J = 8.6, 2.3 Hz, 1H), 7.54−7.50 (m, 1H), 7.41−7.37 (m, 3H), 7.20 (d, J = 2.2 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 4.38 (s, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.9 (C), 169.3 (C), 138.4 (C), 136.9 (C), 134.9 (C), 133.3 (C), 132.3 (CH), 131.2 (CH), 131.2 (CH), 130.4 (CH), 129.8 (CH), 127.2 (CH), 122.7 (C), 116.9 (CH), 56.6 (CH_2); IR (solid) 3253, 2900, 1670, 1505 cm^{-1}.

Diisopropyl 1-(2-(*tert*-Butoxy)-2-oxoethyl)-2-(2-(4-fluorobenzoyl)phenyl)hydrazine-1,2-dicarboxylate 4a. To a stirring solution of sodium hydride (60% mineral oil dispersion, 40 mg, 1.00 mmol, 1.0 equiv) in anhydrous THF (0.5 mL) was added dropwise a solution of diisopropyl 1-(2-(4-fluorobenzoyl)phenyl)hydrazine-1,2-dicarboxylate (0.5 mmol, 1 equiv) predissolved in anhydrous THF (1 mL) under an atmosphere of argon, and the reaction mixture was stirred for 5 min. After this time, to the reaction mixture was added *tert*-butyl bromoacetate (162 μL, 1.10 mmol, 1.1 equiv) dropwise, predissolved in a 1.5 mL anhydrous THF. The reaction mixture was then stirred at 20 °C for 1 h and monitored via TLC till completion and poured over saturated aqueous NH_4Cl (10 mL). The resulting solution was extracted with EtOAc (3 × 15 mL). The combined extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (10−50% EtOAc/petrol) yielded diisopropyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-2-(2-(4-fluorobenzoyl)phenyl)-hydrazine-1,2-dicarboxylate as a yellow oil (230 mg, 0.445 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.88 (m, 3H), 7.49−7.55 (m, 1H), 7.26 (dd, 2H, J = 7.2, 5.9 Hz), 7.09 (t, 2H, J = 8.2 Hz), 5.05 (m, 1H), 4.74 (septet, 1H, J = 6.3 Hz), 4.20−4.60 (m, 2H), 0.96−1.42 (m, 21H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.8 (C), 167.7 (C), 166.6 (d, J_{C-F} = 253.4 Hz, CH), 156.0 (C), 153.8 (C), 139.0 (C), 134.3 (C), 133.3 (CH), 131.8 (CH), 131.6 (CH), 128.9 (CH), 128.2 (CH), 127.0 (CH), 126.3 (CH), 125.9 (CH), 115.5 (d, J_{C-F} = 22.0 Hz, CH), 81.3 (C), 71.0 (CH), 52.5 (CH), 28.2 (CH), 22.2 (CH); IR (thin film) 3341, 2989, 2967, 1743, 1620, 1583, 1523 cm^{-1}; LRMS (ESI) 517 (100, $[M + H]^+$), HRMS (ESI) calcd for $C_{27}H_{34}FN_2O_7$ $[M + H]^+$ 517.2342; observed 517.2348.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b03417.

Copies of characterization data (^{1}H and ^{13}C NMR) of all featured compounds; and detailed experimental procedure, NMR (^{1}H and ^{13}C), IR, LRMS (ESI), and HRMS (ESI) of all featured compounds (PDF)

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Notes

The authors declare no competing financial interest.

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