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Pentafluorophenyl Ester Activation for the Preparation of N,N'-Diaroylhydrazines

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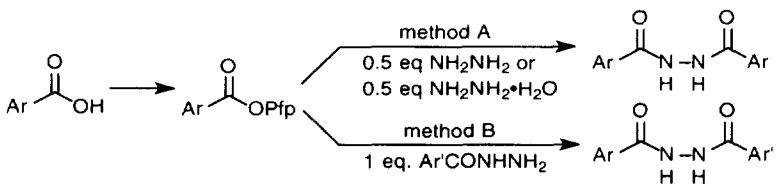
Abstract: Procedures are reported for the preparation of N,N'-diaroylhydrazines using pentafluorophenyl (Pfp) ester activation of aryl carboxylic acids. Mild conditions which avoid intermediate protection of ring substituents, allows the synthesis of both symmetrical and unsymmetrical diaroylhydrazines in high yields. The recent discovery of potent HIV-1 integrase inhibition by N,N'-bis-salicylhydrazine (**1**) highlights the potential importance of this class of compounds. The stability of pre-activated Pfp ester intermediates and the facility with which N,N'-diaroylhydrazines can be synthesized using this procedure (stirring at room temperature in DMF) may make the method particularly attractive for synthesis of hydrazide libraries. Published by Elsevier Science Ltd.

N,N'-Diacylhydrazines (which may also be viewed as N'-acylhydrazides) have value as structural components of heterocyclic ring systems,[1] as peptide bond isosteres in the synthesis azapeptide-based enzyme inhibitors,[2] and as tuberculostatic agents.[3] Recently, N,N'-bis-salicylhydrazine **1**, which had previously been known to chelate a variety of metal ions,[4,5] has been shown to exhibit potent inhibition of the human immunodeficiency virus (HIV) integrase.[6] This enzyme is a potential target for the development of new anti-HIV therapeutics.[7]

A need has therefore arisen for the facile preparation of functionalized N,N'-diaroylhydrazines. Current methods requiring the use of Lewis acids, high temperatures or reactive acyl intermediates[8] are of limited utility, in part due to their incompatibility with certain aryl substituents such as amino, hydroxyl or thiol groups without prior protection. Herein we reported two mild methods using Pfp-activated aroyl esters, which can be run without protection of ancillary functional groups and which are amenable to the preparation of both symmetrical and unsymmetrical diaroylhydrazines.



Scheme 1

It has previously been shown that conversion of amino acids to their pentafluorophenyl (Pfp) esters provides stable compounds which can be isolated or utilized in situ as activated intermediates for the preparation of peptide amides in the presence of free, unprotected hydroxyl groups.[9-11] Due to their "bis-amide" nature, diaroylhydrazines provide a direct analogy for synthesis via Pfp ester activation of corresponding aryl carboxylic acids. In this approach, aroyl Pfp esters can be prepared and isolated without protection of ring-substituted functionality. The Pfp esters formed in this manner can be simply treated with 0.5 equivalents of hydrazine or hydrazine monohydrate (method A, Scheme 1), or alternatively, coupled with 1 equivalent of monohydrazide (method B, Scheme 1, Ar = Ar') to provide symmetrical diaroyl hydrazines (Table 1). Similar yields are obtained whether anhydrous hydrazine or hydrazine monohydrate are employed in method A (Table 1, entries 1 and 2). When method B is employed slightly higher yields are observed than with method A, however this may reflect the fact that method A represents an overall two-step transformation, while method B requires only a single reaction.

Table 1. Comparison of methods A and B for the preparation of symmetrical N,N'-diaroylhydrazines.

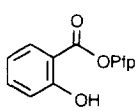
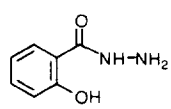
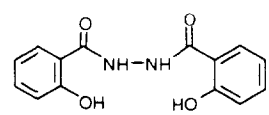
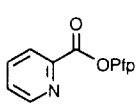
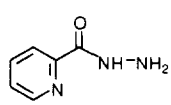
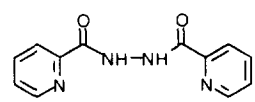
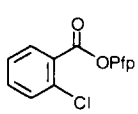
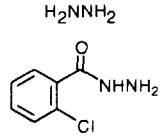
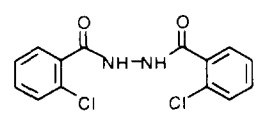
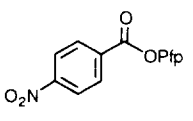
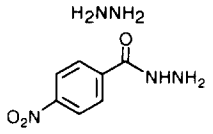
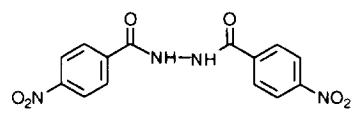
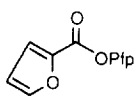
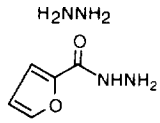
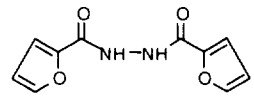
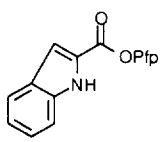
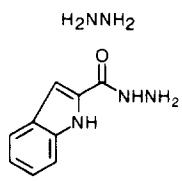
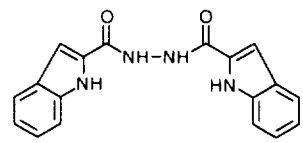
Entry	Pfp ester	Hydrazine or Hydrazide	Method	Product	Yield (%)
1	 **2**	H_2NNH_2 $H_2NNH_2 \cdot H_2O$  **3**	A B	 **1**	90 95 91
2	 **4**	H_2NNH_2 $H_2NNH_2 \cdot H_2O$  **5**	A B	 **6**	91 80 93
3	 **7**	H_2NNH_2  **8**	A B	 **9**	52 75

Table 1. (Continued)

Entry	Pfp ester	Hydrazine or Hydrazide	Method	Product	Yield (%)
4	 **10**	 **11**	A	 **12**	87
			B		95
5	 **13**	 **14**	A	 **15**	55
			B		70
6	 **16**	 **17**	A	 **18**	77
			B		78

Method B is particularly useful for the preparation of unsymmetric N,N'-diaroyl hydrazines (Scheme 1, Ar ≠ Ar'). A variety of different Pfp ester and hydrazide reactants were investigated for this method, with resultant yields of N,N'-diaroyl hydrazines ranging from moderate to high (Table 2). Hydrazides bearing electron-donating substituents gave higher yields of diaroyl hydrazines than those with electron withdrawing substitutes (Table 2, entries 1-9). The Boc protective group does not affect the reaction (Table 2, entry 11) and this may be potentially useful for the incorporation of this methodology in peptide synthesis.

One limitation of both methods A and B may be the availability or ease of synthesis of appropriate starting aroyl Pfp esters and aromatic monohydrazides. For example we were unsuccessful in our attempts to prepare 4-hydroxy-7-trifluoromethyl-3-quinoline carboxylic acid Pfp ester and its corresponding monohydrazide. However, the utility of the approach has been demonstrated by the preparation of several diaroyl hydrazines bearing a wide range of structures, and further application of these methods is currently in progress. The utilization of stable, pre-activated intermediates under mild conditions may have particular applicability for the synthesis of hydrazide libraries.

Table 2. Examples of unsymmetrical N,N'-diaroylhydrazines prepared using method B.

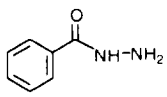
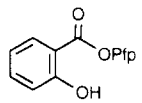
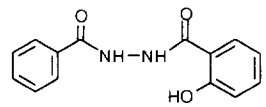
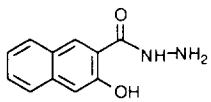
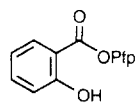
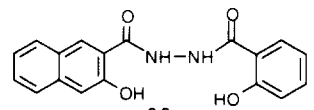
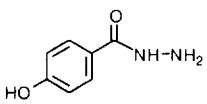
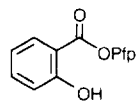
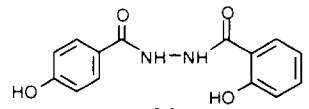
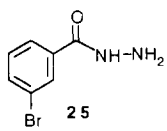
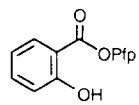
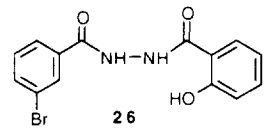
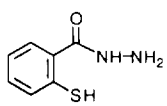
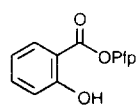
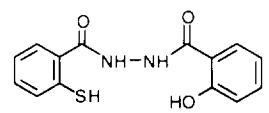
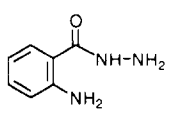
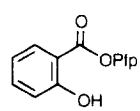
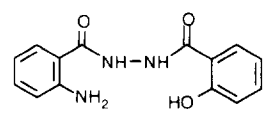
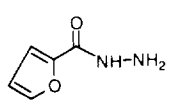
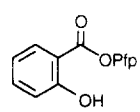
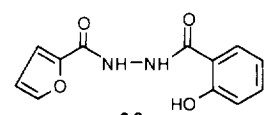
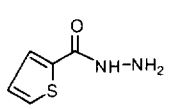
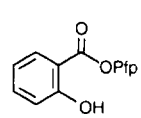
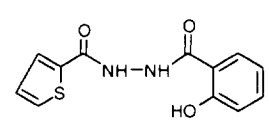
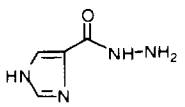
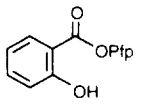
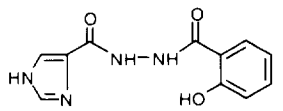
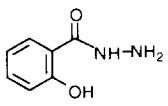
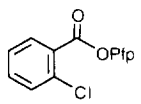
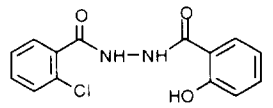
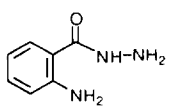
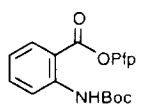
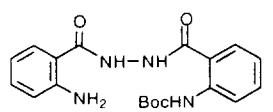
Entry	Hydrazide	Pfp ester	Product	Yield (%)
1	 **19**	 **2**	 **20**	75
2	 **21**	 **2**	 **22**	58
3	 **23**	 **2**	 **24**	98
4	 **25**	 **2**	 **26**	75
5	 **27**	 **2**	 **28**	89
6	 **29**	 **2**	 **30**	97
7	 **31**	 **2**	 **32**	62
8	 **33**	 **2**	 **34**	52

Table 2. (Continued)

Entry	Hydrazide	Pfp ester	Product	Yield (%)
9	 **35**	 **2**	 **36**	74
10	 **3**	 **7**	 **37**	77
11	 **29**	 **38**	 **39**	92

Experimental

Melting points were taken on a Mel Temp II melting point apparatus and are uncorrected. Elemental analyses were obtained from Atlantic Microlab Inc., Norcross, GA. IR (KBr) spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer and ^{1}H NMR data were obtained on a Bruker AC250 (250 MHz) instrument. Fast atom bombardment mass spectra (FABMS) were acquired with a VG Analytical 7070E mass spectrometer under the control of a VG 2035 data system. Flash column chromatography was performed using E. Merck silica gel 60 (particle size, 0.04 - 0.063 mm).

Preparation of Pfp Esters

General method. A mixture of aromatic acid (10 mmol), pentafluorophenol (11 mmol) and dicylcohexylcarbodiimide (DCC) (10 mmol) in anhydrous dioxane (40 mL) was stirred at room temperature (overnight). Dicyclohexyl urea was removed by filtration through celite, and the filtrate taken to dryness and purified directly by crystallization or by silica gel chromatography.

Salicylic acid pentafluorophenyl ester (2). A mixture of salicylic acid (4.14 g, 30 mmol), pentafluorophenol (5.52 g, 33 mmol) and DCC (6.3 g, 30 mmol) in dioxane (180 mL) was stirred at room temperature (overnight). Dicyclohexyl urea was removed by filtration through celite, and the filtrate taken to dryness. Residue was crystallized from ether:hexane to provide **2** as a white solid (4.56 g, 50% yield), mp 111-111.5 °C. ^{1}H NMR ($CDCl_3$) δ 9.83 (s, 1H), 8.06 (dd, J = 8.1, 1.6 Hz, 1H), 7.63-7.56 (m, 1H), 7.08-6.97 (m, 2H).

Picolinic acid pentafluorophenyl ester (4). Reaction of picolinic acid (1.23 g, 10 mmol) with pentafluorophenol (1.84 g, 10 mmol) in dioxane (30 mL) as described above in the general method, with purification by silica gel chromatography followlowed by crystallization provided **4** as a white solid (1.52 g, 53%), mp 62-64 °C (ether:hexane). ^{1}H NMR ($CDCl_3$) δ 8.87 (d, J = 4.5 Hz, 1H), 8.29 (d, J = 7.9 Hz, 1H), 7.99-7.92 (m, 1H), 7.64-7.56 (m, 1H).

2-Chlorobenzoic acid pentafluorophenyl ester (7). Reaction of 2-chlorobenzoic acid (1.56 g, 10 mmol) with pentafluorophenol (2 g, 11 mmol) in dioxane (40 mL) as described above, provided **7** as a white solid (2.17 g, 65%), mp 44-46 °C (ether:hexane). ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 3.6 Hz, 1H), 7.45-7.38 (m, 1H).

4-Nitrobenzoic acid pentafluorophenyl ester (10). Reaction of 4-nitrobenzoic acid (1.67 g, 10 mmol) with pentafluorophenol (2 g, 11 mmol) in dioxane (40 mL) as described above in the general method provided **10** as a white solid (2.17 g, 65%), mp 123-125 °C (ether:hexane). ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 4H).

2-Furoic acid pentafluorophenyl ester (13). Reaction of 2-furoic acid (1.12 g, 10 mmol) with pentafluorophenol (2 g, 11 mmol) in dioxane (40 mL) as described above provided **13** as a white solid (2.47 g, 89%), mp 53-55 °C (ether:hexane). ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 5.1 Hz, 1H), 7.49 (d, J = 3.6 Hz, 1H), 6.67-6.63 (m, 1H).

Indole-2-carboxylic acid pentafluorophenyl ester (16). Reaction of indole-2-carboxylic acid (1.6 g, 10 mmol) with pentafluorophenol (2 g, 11 mmol) in dioxane (40 mL) as described above provided **16** as a white solid (3.13 g, 96%), mp 172-174 °C (ether:hexane). ^{1}H NMR ($CDCl_3$) δ 8.98 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.48-7.37 (m, 2H), 7.2-7.18 (m, 1H).

N-(*tert*-Butoxycarbonyl)anthranilic acid pentafluorophenyl ester (38). Anthranilic acid (2.74 g, 20 mmol) was added to a 10% solution of triethylamine in methanol (30 mL). To this mixture was added di-*t*-butyl dicarbonate (4.4 g, 40 mmol) with vigorous stirring and the mixture then heated to 40 - 50 °C (2 h). Solvent was removed and the residue was stirred with ice-cold dilute hydrochloric acid (pH ~ 2; 10 min) and extracted immediately with EtOAc (4 x 50 mL) dried (Na_2SO_4) and taken to dryness. The resulting oil was crystallized (ether:hexane) to provide N-(*tert*-butoxycarbonyl)anthranilic acid as white solid (3.82 g, 81%), mp 146-148.5 °C (lit.[12] 155.5-157.0 °C). ^{1}H NMR ($CDCl_3$) δ 10.03 (s, 1H), 8.45 (d, J = 8.6 Hz, 1H), 8.09 (dd, J = 8.0, 1.4 Hz, 1H), 7.58-7.51 (m, 1H), 7.05-6.99 (m, 1H), 1.53 (s, 9H). A portion of this compound (2.37 g, 10 mmol) was reacted with pentafluorophenol (1.84 g, 10 mmol) in dioxane (30 mL) as described above and purified by silica gel chromatography (hexane) to provide **38** as a crystalline white solid (2.5 g, 62%), mp 88-88.5 °C (ether:hexane). ^{1}H NMR ($CDCl_3$) δ 9.72 (s, 1H), 8.54 (d, J = 8.7 Hz, 1H), 8.22 (dd, J = 8.1, 1.3 Hz, 1H), 7.67-7.61 (m, 1H), 7.13-7.06 (m, 1H), 1.49 (s, 9H).

Preparation of Symmetrical N,N'-Diaroylhydrazines via Method A

General method A. A solution of pentafluorophenyl ester (1 mmol) and 0.5 mmol of either anhydrous hydrazine (160 μL of a 10% solution of anhydrous hydrazine in anhydrous DMF) or hydrazine monohydrate (24 μL) in DMF (3 mL) was stirred at room temperature (overnight). Solvent was removed under reduced pressure and residue either crystallized directly from EtOAc, or purified by silica gel chromatography prior to crystallization.

N,N'-Bis-salicylhydrazine (1). Reaction of salicylic acid pentafluorophenyl ester **2** (304 mg, 1.0 mmol) with anhydrous hydrazine or hydrazine monohydrate as described in the general method A, provided **1** as a white solid (123 mg, 90% and 130 mg, 95%, respectively), mp 315-316 °C (EtOAc) (lit.[5] 302 °C). ^{1}H NMR (DMSO-d_6) δ 11.78 (s, 2H), 10.89 (s, 2H), 7.92 (dd, J = 7.8, 1.3 Hz, 2H), 7.49-7.42 (m, 2H), 7.0-6.94 (m, 4H); IR (KBr) 3088, 1654, 1605, 1484, 1234, 754; FABMS *m/z* 273 (MH^+). Analysis ($C_{14}H_{12}N_2O_4$): C, 61.76; H, 4.44; N, 10.29. Found: C, 61.66; H, 4.51; N, 10.37.

N,N'-Bis-picolinoylhydrazine (6). Reaction of picolinic acid pentafluorophenyl ester **4** (289 mg, 1.0 mmol) with anhydrous hydrazine or hydrazine monohydrate as described in the general method A, provided **6** as a white solid (110 mg, 91% and 96 mg, 80%, respectively) mp 224-225 °C (EtOAc). ^{1}H NMR (DMSO-d_6) δ 10.63 (s, 2H), 8.70 (d, J = 4.8 Hz, 2H), 8.05-8.04 (m, 4H), 7.69-7.63 (m, 2H); IR (KBr) 3321, 1676, 1560, 1482; FABMS *m/z* 243 (MH^+). Analysis ($C_{12}H_{10}N_4O_2$): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.45; H, 4.17; N, 23.07.

N,N'-Bis-2-chlorobenzoylhydrazine (9). Reaction of 2-chlorobenzoic acid pentafluorophenyl ester **7** (322 mg, 1.0 mmol) with anhydrous hydrazine as described in the general method A, provided **9** as a white solid (81 mg, 52%), mp 221-222 °C (EtOAc:hexane). ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 2H), 7.56-7.63 (m, 8H); Analysis ($C_{14}H_{10}N_2Cl_2O_2$): C, 54.39; H, 3.26; N, 9.06. Found: C, 54.34; H, 3.28; N, 9.00.

N,N'-Bis-4-nitrobenzoylhydrazine (12). Reaction of 4-nitrobenzoic acid pentafluorophenyl ester **10** (333 mg, 1.0 mmol) with anhydrous hydrazine as described in the general method A, provided **12** as a light yellow solid (144 mg, 87%), mp 297-298 °C (EtOAc). ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 2H), 8.39 (d, J = 7.7 Hz, 4H), 8.15 (d, J = 7.7 Hz, 4H); Analysis ($C_{14}H_{10}N_4O_6$): C, 50.92; H, 3.05; N, 16.96. Found: C, 51.02; H, 3.02; N, 16.93.

N,N'-Bis-2-furoylhydrazine (15). Reaction of 2-furoic acid pentafluorophenyl ester **13** (278 mg, 1.0 mmol) with anhydrous hydrazine as described in the general method A, provided **15** as a white solid (60 mg, 55%), mp 238-239 °C (EtOAc). ^{1}H NMR (DMSO-d_6) δ 10.34 (s, 2H), 7.91 (s, 2H), 7.25 (d, J = 5.5 Hz, 2H), 6.68-6.66 (m, 2H); Analysis ($C_{10}H_8N_2O_4$): C, 54.55; H, 3.66; N, 12.72. Found: C, 54.48; H, 3.71; N, 12.78.

N,N'-Bis-(indole-2-carboxoyl)hydrazine (18). Reaction of indole-2-carboxylic acid pentafluorophenyl ester **16** (327 mg, 1.0 mmol) with anhydrous hydrazine as described in the general method A, provided **18** as a white solid (123 mg, 77%), mp 356.5-357.5 °C (EtOAc). ^{1}H NMR (DMSO-d_6) δ 11.76 (s, 2H), 10.55 (s, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.29 (s, 2H), 7.25-7.19 (m, 2H), 7.1-7.04 (m, 2H); Analysis ($C_{18}H_{14}N_4O_2$): C, 67.92; H, 4.43; N, 17.60. Found: C, 68.01; H, 4.45; N, 17.53.

Preparation of aroylhydrazides

General method. A mixture of aromatic carboxylic acid methyl or ethyl ester and hydrazine monohydrate neat or in ethanol was heated under reflux overnight. After cooling to room temperature, resulting white solids were collected by filtration and dried in vacuo.

Thiosalicylhydrazide (27). Reaction of methyl thiosalicylate (3.36g, 20 mmol) with hydrazine monohydrate (3 mL) as described in the general method provided **27** (3.29 g, 98%), mp 210-211 °C. ^{1}H NMR (DMSO-d_6) δ 9.85 (br s, 1H), 7.64-7.57 (m, 2H), 7.47-7.41 (m,1H), 7.3-7.24 (m, 1H), 4.62 (br s, 2H).

2-Aminobenzoic acid hydrazide (29). Reaction of ethyl 2-aminobenzoate (1.65 g, 10 mmol) with hydrazine monohydrate (1 mL) as described in the general method provided **29** (0.75 g, 50%), mp 118-120 °C (lit.[13] 117-118 °C). ^{1}H NMR (DMSO-d_6) δ 9.45 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.14-7.08 (m, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.49-6.43 (m, 1H), 6.31 (s, 2H), 4.35 (s, 2H). Analysis ($C_7H_9N_3O$): C, 55.62; H, 6.00; N, 27.80. Found: C, 55.55; H, 6.01; N, 27.92.

Indole-2-carboxylic acid hydrazide (17). Reaction of ethyl indole-2-carboxylate (1.89 g, 10 mmol) with hydrazine monohydrate (2 mL) as described in the general method provided **17** (1.71 g, 98%), mp 250-252.5 °C. ^{1}H NMR (DMSO-d_6) δ 11.58 (s, 1H), 9.76 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.19-7.13 (m, 1H), 7.07 (s, 1H), 7.04-6.98 (m, 1H), 4.5 (s, 2H). Analysis ($C_9H_9N_3O$): C, 61.70; H, 5.18; N, 23.99. Found: C, 61.80; H, 5.20; N, 24.06.

4-Imidazole carboxylic acid hydrazide (35). Reaction of methyl 4-imidazolecarboxylate (1 g, 8 mmol) with hydrazine monohydrate (2 mL) in ethanol (15 mL) as described in the general method provided **35** (0.91 g, 89%), mp 203-205 °C. ^{1}H NMR (DMSO-d_6) δ 9.05 (s, 1H), 7.69 (d, J = 0.8 Hz, 1H), 7.59 (d, J = 0.8

Hz, 1H), 4.32 (br s, 2H), 3.31 (br s, 1H). Analysis ($C_4H_6N_4O \cdot H_2O$): C, 35.09; H, 5.30; N, 40.92. Found: C, 35.23; H, 5.20; N, 40.70.

Preparation of N,N'-diaroylhydrazines via method B

General method B. A solution of aromatic hydrazide (1 mmol) and pentafluorophenyl ester (1 mmol) in DMF (3 mL) was stirred at room temperature (overnight). Solvent was removed under reduced pressure and residue either crystallized directly from EtOAc, or purified by silica gel chromatography prior to crystallization.

Symmetrical Hydrazines:

N,N'-Bis-salicylhydrazine (1). Reaction of commercially available salicylhydrazide **3** (304 mg, 2 mmol) with salicylic acid pentafluorophenyl ester **2** (608 mg, 2mmol) as described in general method B provided **1** (494 mg, 91%).

N,N'-Bis-picolinoylhydrazine (6). Reaction of commercially available picolinic acid hydrazide **5** (137 mg, 1 mmol) with picolinic acid pentafluorophenyl ester **4** (289 mg, 1 mmol) as described in general method B provided **6** (225 mg, 93%).

N,N'-Bis-(2-chlorobenzoyl)hydrazine (9). Reaction of commercially available 2-chlorobenzoic acid hydrazide **8** (170 mg, 1 mmol) with 2-chlorobenzoic acid pentafluorophenyl ester **7** (322 mg, 1.0 mmol) as described in general method B provided **9** (232 mg, 74%).

N,N'-Bis-(4-nitrobenzoyl)hydrazine (12). Reaction of commercially available 4-nitrobenzoic acid hydrazide **11** (181 mg, 1 mmol) with 4-nitrobenzoic acid pentafluorophenyl ester **10** (333 mg, 1.0 mmol) as described in general method B provided **12** (312 mg, 95%).

N,N'-Bis-(2-furoyl)hydrazine (15). Reaction of commercially available 2-furoic acid hydrazide **14** (126 mg, 1 mmol) with 2-furoic acid pentafluorophenyl ester **13** (278 mg, 1.0 mmol) as described in general method B provided **15** (154 mg, 70%).

N,N'-Bis-(indole-2-carboxoyl)hydrazine (18). Reaction of indole-2-carboxylic acid hydrazide **17** (175 mg, 1 mmol) with indole-2-carboxylic acid pentafluorophenyl ester **16** (327 mg, 1.0 mmol) as described in general method B provided **18** (249 mg, 78%).

Unsymmetrical Hydrazines:

N-Benzoyl-N'-salicylhydrazine (20). Reaction of commercially available benzoic hydrazide **19** (136 mg, 1 mmol) with salicylic acid pentafluorophenyl ester **2** (304 mg, 1 mmol) as described in general method B provided **20** as a white solid (191 mg, 75%), mp 260-260.5 °C (EtOAc) (lit.[14] 254-257 °C). ^{1}H NMR

(DMSO-d_6) δ 11.95 (s, 1H), 10.68 (s, 2H), 7.93-7.91 (m, 3H), 7.64-7.44 (m, 4H), 6.99-6.93 (m, 2H); IR (KBr) 3304, 1654, 1607, 1544, 1282; FABMS *m/z* 257 (MH^+); Analysis ($C_{14}H_{12}N_2O_3$): C, 65.62; H, 4.72; N, 10.93. Found: C, 65.58; H, 4.74; N, 11.00.

N-(3-Hydroxy-2-naphthoyl)-N'-salicylhydrazine (22). Reaction of commercially available 3-hydroxy-2-naphthoic hydrazide **21** (202 mg, 1 mmol) with salicylic acid pentafluorophenyl ester **2** (304 mg, 1 mmol) as described in general method B provided **22** as a white solid (188 mg, 58%), mp 302-303 °C (EtOAc). ^1H NMR (DMSO-d_6) δ 11.86 (br s, 1H), 11.49 (br s, 1H), 11.08 (br s, 2H), 8.56 (s, 1H), 7.98-7.92 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.76-7.43 (m, 2H), 7.4-7.36 (m, 1H), 7.34 (s, 1H), 7.02-6.94 (m, 2H); IR (KBr) 3118, 1654, 1604, 1560, 1227; FABMS *m/z* 322 (M-H); Analysis ($C_{18}H_{14}N_2O_4$•0.25 H_2O): C, 66.15; H, 4.47; N, 8.57. Found: C, 66.37; H, 4.67; N, 8.37.

N-(4-Hydroxybenzoyl)-N'-salicylhydrazine (24). Reaction of commercially available 4-hydroxybenzoic hydrazide **23** (154 mg, 1 mmol) with salicylic acid pentafluorophenyl ester **2** (304 mg, 1 mmol) as described in general method B provided **24** as a white solid (267 mg, 98%), mp 298-299 °C (EtOAc). ^1H NMR (DMSO-d_6) δ 11.98 (s, 1H), 10.6 (s, 1H), 10.39 (s, 1H), 10.12 (s, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.8 (d, *J* = 8.6 Hz, 2H), 7.48-7.43 (m, 1H), 6.98-6.92 (m, 2H), 6.81 (d, *J* = 8.6Hz, 2H); Analysis ($C_{14}H_{12}N_2O_4$): C, 61.76; H, 4.44; N, 10.29. Found: C, 61.58; H, 4.63; N, 10.46.

N-(3-Bromobenzoyl)-N'-salicylhydrazine (26). Reaction of commercially available 3-bromobenzoic hydrazide **25** (215 mg, 1 mmol) with salicylic acid pentafluorophenyl ester **2** (304 mg, 1 mmol) as described in general method B provided **26** as a white solid (250 mg, 75%), mp 231-232 °C (EtOAc). ^1H NMR (DMSO-d_6) δ 11.86 (s, 1H), 10.82 (s, 1H), 10.71 (s, 1H), 8.09 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.84-7.8 (m, 1H), 7.54-7.44 (m, 2H), 7.0-6.93 (m, 2H); Analysis ($C_{14}H_{11}N_2O_3Br$): C, 50.17; H, 3.31; N, 8.36. Found: C, 50.21; H, 3.38; N, 8.46.

N-Thiosalicyl-N'-salicylhydrazine (28). Reaction of thiosalicylhydrazide **27** (168 mg, 1 mmol) with salicylic acid pentafluorophenyl ester **2** (304 mg , 1 mmol) as described in general method B provided **28** as a white solid (253 mg, 89%), mp 226-229 °C (EtOAc). ^1H NMR (DMSO-d_6) δ 11.93 (s, 1H), 10.85 (s, 1H), 10.79 (s, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.6-7.36 (m, 3H), 7.01-6.94 (m, 2H); IR (KBr) 3246, 1654, 1560, 1230, 750; FABMS *m/z* 287 (M-H); Analysis ($C_{14}H_{12}N_2O_3S$): C, 58.32; H, 4.20; N, 9.72. Found: C, 58.06; H, 4.17; N, 9.64.

N-(2-Aminobenzoyl)-N'-salicylhydrazine (30). Reaction of 2-aminobenzoic acid hydrazide **29** (151 mg, 1 mmol) with salicylic acid pentafluorophenyl ester **2** (304 mg , 1 mmol) as described in general method B provided **30** as a white solid (262 mg, yield: 97%), mp 196-197 °C (EtOAc). ^1H NMR (DMSO-d_6) δ 11.99 (s,

1H), 10.56 (s, 1H), 10.22 (br s, 1H), 7.94-7.91 (m, 1H), 7.63-7.6 (m, 1H), 7.48-7.43 (m, 1H), 7.23-7.17 (m, 1H), 6.98-6.92 (m, 2H), 6.76-6.72 (m, 1H), 6.58-6.52 (m, 1H), 6.45 (br s, 2H); IR (KBr) 3568, 3311, 1654, , 1624, 1560, 1269; FABMS *m/z* 271 (MH^+).

N-(2-Furoyl)-N'-salicylhydrazine (32). Reaction of commercially available 2-furoic hydrazide **31** (126 mg, 1 mmol) with salicylic acid pentafluorophenyl ester **2** (304 mg, 1 mmol) as described in general method B provided **32** as a white solid (155 mg, 62%), mp 206-207 °C (EtOAc). ^{1}H NMR (DMSO-d_6) δ 11.9 (s, 1H), 10.6 (s, 1H), 10.14 (s, 1H), 7.93 (s, 1H), 7.9 (d, J = 7.8 Hz, 1H), 7.49-7.43 (m, 1H), 7.28 (d, J = 3.4 Hz, 1H), 6.98-6.6.92 (m, 2H), 6.7-6.69 (m, 1H); Analysis ($C_{12}H_{10}N_2O_4$): C, 58.54; H, 4.09; N, 11.38. Found: C, 58.32; H, 4.21; N, 11.09.

N-(2-Thiophenecarboxoyl)-N'-salicylhydrazine (34). Reaction of commercially available 2-thiophenecarboxylic hydrazide **33** (142 mg, 1 mmol) with salicylic acid pentafluorophenyl ester **2** (304 mg, 1 mmol) as described in general method B provided **34** as a white solid (135 mg, 52%), mp 227.5-228.5 °C (EtOAc). ^{1}H NMR (DMSO-d_6) δ 11.85 (s, 1H), 10.67 (s, 1H), 10.64 (s, 1H), 7.91-7.86 (m, 3H), 7.49-7.43 (m, 1H), 7.24-7.2 (m, 1H), 6.99-6.92 (m, 2H); Analysis ($C_{12}H_{10}N_2SO_4$): C, 54.95; H, 3.84; N, 10.68. Found: C, 54.77; H, 4.01; N, 10.48.

N-(4-Imidazolecarboxoyl)-N'-salicylhydrazine (36). Reaction of 4-imidazolecarboxylic hydrazide **35** (127 mg, 1 mmol) with salicylic acid pentafluorophenyl ester **2** (304 mg, 1 mmol) as described in general method B provided **36** as a white solid (182 mg, 74%), mp 257-259 °C (EtOAc). ^{1}H NMR (DMSO-d_6) δ 12.88 (br s, 1H), 12.07 (br s, 1H), 10.58 (br s, 1H), 9.99 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.48-7.42 (m, 1H), 6.97-6.9 (m, 2H).

N-(2-Chlorobenzoyl)-N'-salicylhydrazine (37). Reaction of salicylic hydrazide **3** (152 mg, 1 mmol) with 2-chlorobenzoic acid pentafluorophenyl ester **7** (332 mg, 1 mmol) as described in general method B provided **37** as a white solid (192 mg, 77%), mp 194-196 °C (EtOAc:hexane). ^{1}H NMR (DMSO-d_6) δ 11.95 (br s, 1H), 10.78 (br s, 1H), 10.65 (s, 1H), 7.94 (dd, J = 7.5, 1.2 Hz, 1H), 7.59 (m, 5H), 7.0-6.92 (m, 2H); Analysis ($C_{14}H_{11}N_2ClO_3$): C, 57.84; H, 3.81; N, 9.64. Found: C, 57.75; H, 3.84; N, 9.69.

N-2-(*tert*-Butoxycarbonylamino)benzoyl-N'-2-aminobenzoylhydrazine (39). Reaction of 2-aminobenzoic acid hydrazide **29** (206 mg, 0.5 mmol) and N-(*tert*-butoxycarbonyl)anthranilic acid pentafluorophenyl ester **38** (75 mg, 0.5 mmol) as described in general method B, followed by silica gel chromatographic purification (EtOAc:hexane, 1:1) provided **39** as a syrup (171 mg, 92%). ^{1}H NMR (DMSO-d_6) δ 10.57 (s, 1H); 10.26 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.56-7.5 (m, 1H), 7.24-7.08 (m, 2H), 6.75 (d, J = 8.2 Hz, 1H), 6.58-6.55 (m, 1H), 6.52 (s, 2H), 1.45 (s, 9H).

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