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Access to 2,5-disubstituted furans through a Passerini-Smiles/furyl rearrangement pathway

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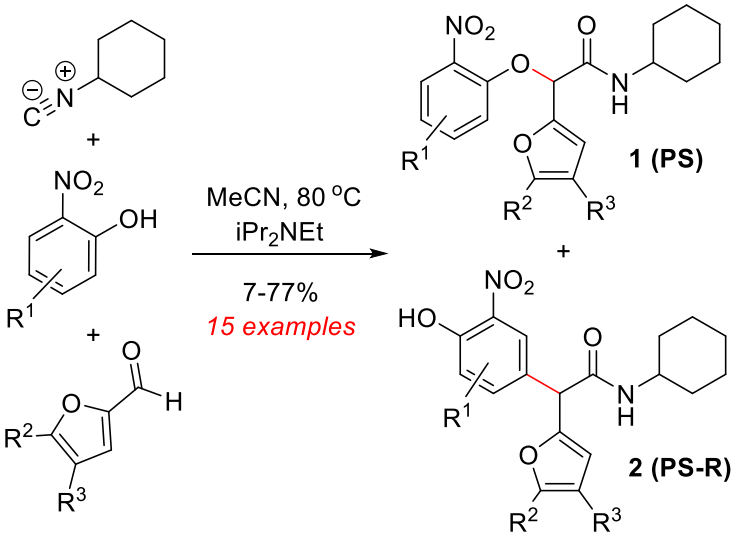
Abstract

A one-pot tandem route to functionalized 2,5-disubstituted furans possessing 4-hydroxy-3-nitrophenyl substituents has been achieved through a standard Passerini-Smiles reaction, followed by an unexpected furyl cation-driven skeletal rearrangement. Substitution of the 2-furaldehyde or 2-nitrophenol component determines whether a standard Passerini-Smiles reaction (PS) is followed by rearrangement to produce a rearranged PS-R product. This rearrangement has been confirmed through isolation of the PS product, followed by microwave irradiation to obtain conversion to the PS-R product.



Keywords: Passerini-Smiles, multicomponent reaction, isocyanide, furaldehyde

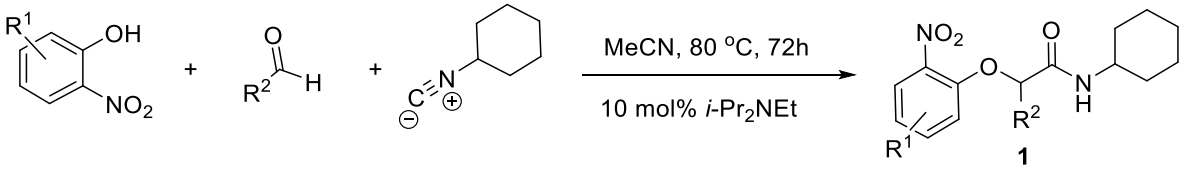
Introduction

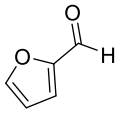
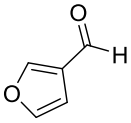
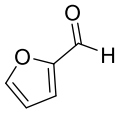
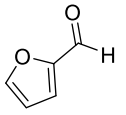
Isocyanide-based multicomponent coupling reactions (IMCRs) provide access to a range of molecularly diverse products from simple starting materials.[1-3] These reactions are often combined with compatible secondary reactions in tandem processes, to prepare libraries of heterocycles.[4-6] The three-component Passerini-Smiles coupling (PS-3CC) of an electron deficient phenol, an aldehyde, and isocyanide is an efficient method for the preparation of α-aryloxyamides.[7,8] While a range of aldehydes are tolerated, previous studies have shown limited success for reactions that used α,β-unsaturated aldehydes or 2-furaldehyde as reaction components.[9-11] Optimized reaction conditions for the Passerini-Smiles reaction used neat conditions with DABCO or *N*,*N*-dimethypiperazine as additives;[12] however, α,β-unsaturated aldehydes remained unsuccessful.[13] However, Dai reported successful Passerini-Smiles reactions with 2-furaldehyde and *trans*-cinnamaldehyde, in the presence of acetonitrile and i-Pr_2NEt (10 mol%).[14] We were interested in exploring furaldehyde-derived components to develop tandem processes that involved Passerini-Smiles reactions. During these studies, we observed an unexpected post-condensation rearrangement to generate 2,5-disubstituted furans possessing 4-hydroxy-3-nitrophenyl substituents.

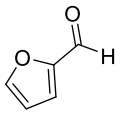
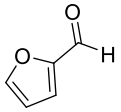
Results and Discussion

Application of Dai's optimized conditions[14] led to good conversion into Passerini-Smiles products **1** (PS-3CC) for reactions that used substituted 2-nitrophenol components. 3-Furaldehyde was also successful as a reaction component under these conditions (entry 2). Several 4- and 5-substituted nitrophenols were also competent phenols, but 2-hydroxy-3-nitropyridine provided only trace conversion to the desired Passerini-Smiles product (not shown).

Table 1. Synthesis of α-aryloxyamides from Passerini-Smiles reactions



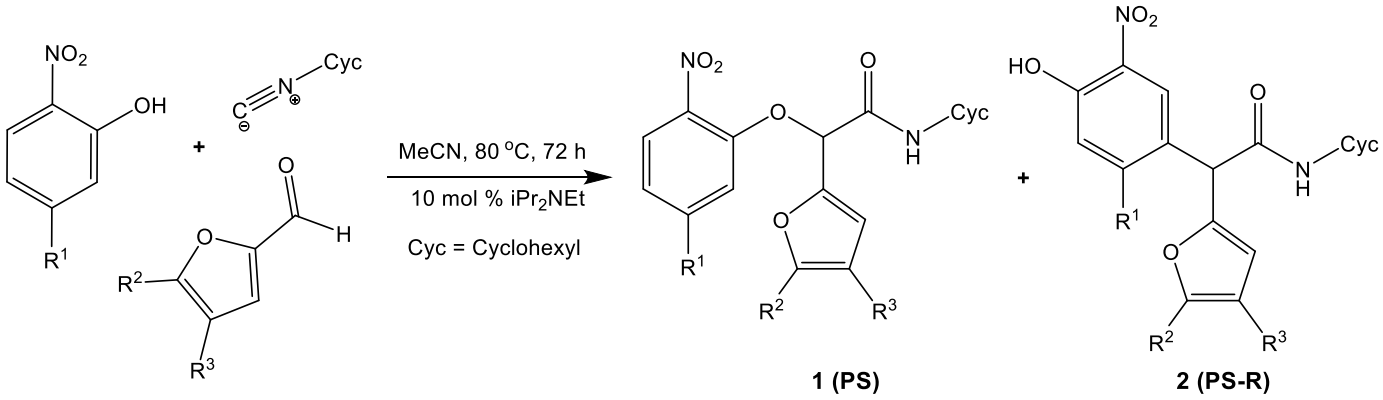
Entry	R^1	R^2-CHO	Product	Yield (%)[a,b]
1	H		**1a**	74
2	H		**1b**	52
3	4-CH_3		**1c**	50
4	4-OCH_3		**1d**	31

5	4-F		**1e**	60
6	5-Br		**1f**	77

[a] Reactions used 1:1.3:1.5 ratio phenol : aldehyde : isocyanide. [b] Isolated yield after column chromatography.

However, an unexpected rearrangement was observed when substitution was examined for 2-furaldehyde components (Table 2). While the Passerini-Smiles reaction tolerated 4-bromo and 2-chloro substitutions on 2-furaldehyde (31-64%, entries 1 and 2), other substitutions at the 5-position led to low conversions with formation of a new rearranged product (**2**). Use of *tert*-butyl or benzyl isocyanide components led to lower overall yields (not shown).

Table 2. Aldehyde and phenol variations to produce PS (**1**) and rearranged PS-R products (**2**)



Entry	R^1	R^2	R^3	Products	PS (**1**) : PS-R (**2**) Ratio[a]	Yield (%)[b,c]
1	H	H	Br	**1g**	PS only	64
2	H	Cl	H	**1h**	PS only	31
3	H	I	H	**1i : 2b**	7 : 2	25
4	H	CH_3	H	**1j : 2c**	1 :17	18
5	H	CH_3	CH_3	**2d**	PS-R only	27
6	5-Br	Cl	H	**1k**	PS only	7
7	5-Br	I	H	**1l : 2e**	7 : 2	17
8	5-Br	CH_3	H	**1m : 2f**	1 :12	58
9	5-Br	CH_3	CH_3	**2g**	PS-R only	26

[a] Ratio calculated from ^{1}H NMR analysis when products could not be separated. [b] Reactions used 1:1.3:1.5 ratio phenol : aldehyde : isocyanide. [c] Isolated yield after column chromatography.

A similar rearrangement to an alternate PS-R product (**3**) was observed when 2-allyl-6-nitrophenol was used in the Passerini-Smiles reaction (Figure 1), generating a 2,5-disubstituted furan possessing a functionalized 4-hydroxy-3-nitrophenyl substituent. When the reaction was performed in standard conditions, acetonitrile in the presence of iPr_2NEt, no product was isolated. In methanol at 50°C for 48h, Passerini-Smiles

product (**1n**) was the major product (**1n**:**3** 26:3); however, **3** was the major product isolated for the reaction run at 65°C for 48h.

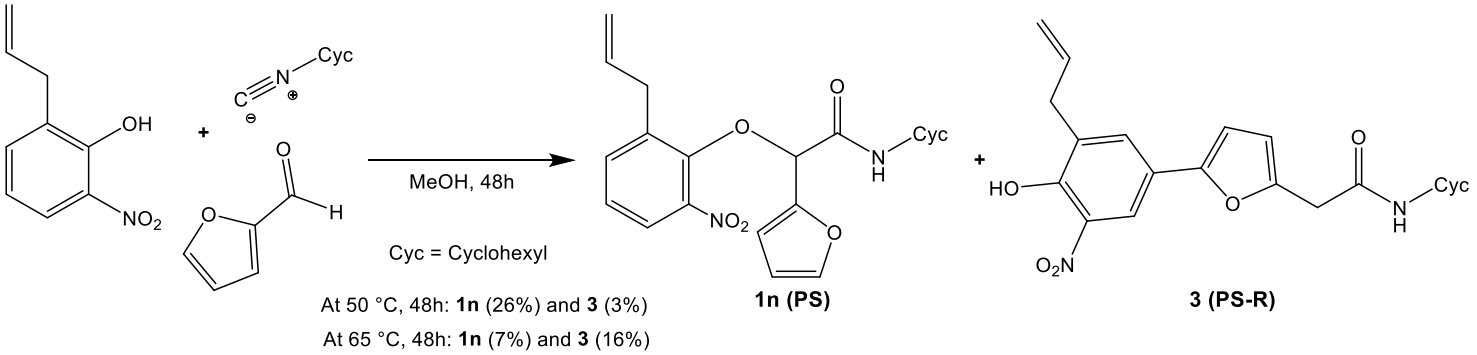


Figure 1: Use of 2-allyl-6-nitrophenol in the Passerini-Smiles reaction

Reaction monitoring by ^{1}H NMR supported our understanding that products PS-R **2** and **3** were generated from rearrangement of the initially formed Passerini-Smiles products (**1**). To support these observations, **1n** was isolated and submitted to microwave irradiation (120°C, methanol) to provide direct conversion to the PS-R product **3** in 52% yield (Figure 2). The remainder of the recovered mass was composed of unreacted starting material and a small amount of the cleaved 2-allyl-6-nitrophenol component.

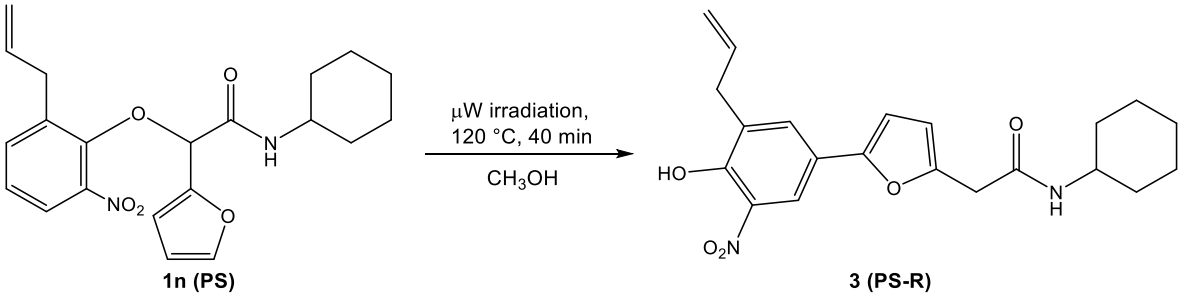


Figure 2: Microwave assisted rearrangement of isolated PS product (**1n**) to PS-R product (**3**)

This rearrangement can be understood to occur through furan participation in cleavage of the α-aryloxy group, generating a reactive furyl carbocation that can undergo reaction with the phenolate species at either the α-carbon to the amide (when R^2 = CH_3 or I, product **2**) or the 5-position of the furan (when R^2 = H, **3**) when a hindered 2,6-substituted phenol was used (Figure 3).

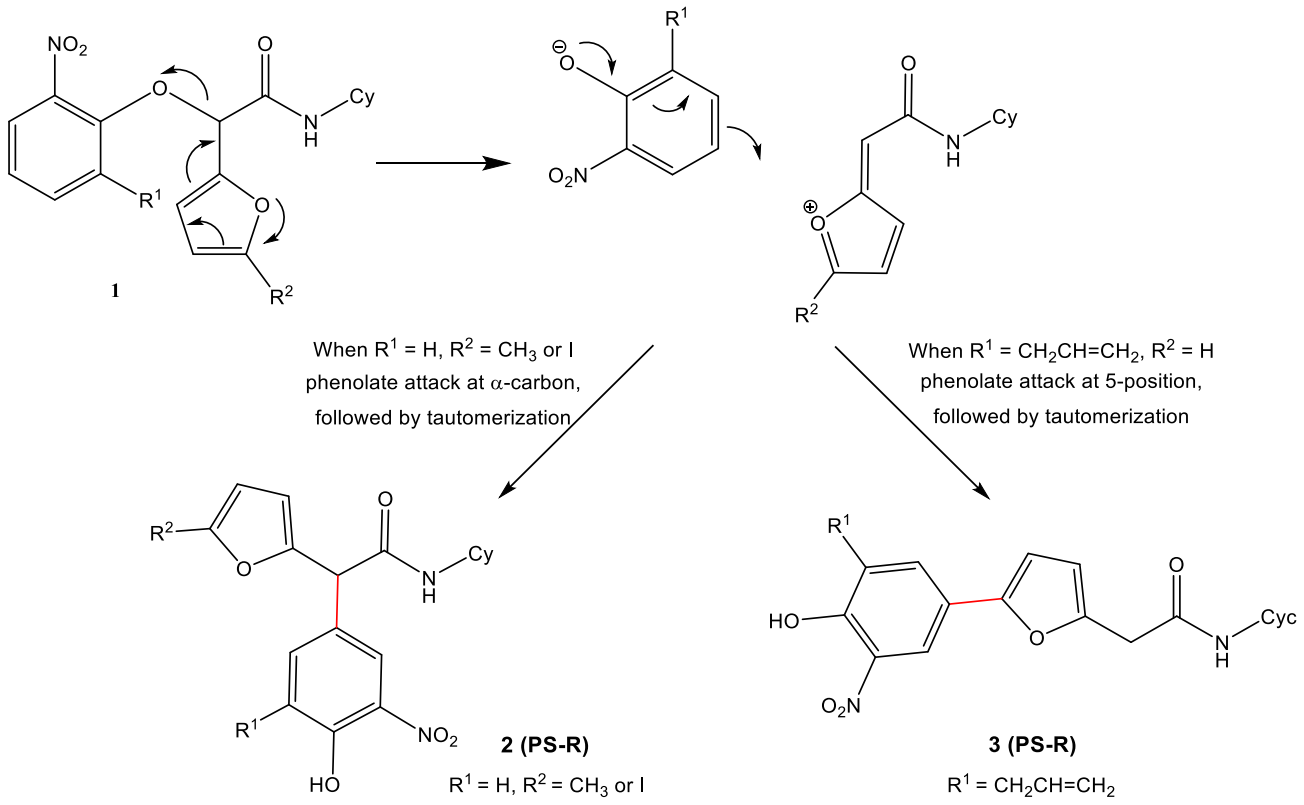


Figure 3: Proposed pathway for furyl cation-derived rearrangement of Passerini-Smiles products

Conclusions

In summary, we have reported successful use of substituted furaldehyde components in the Passerini-Smiles three-component coupling. Under the reaction conditions, we observed a rearrangement process that led to formation of 2,5-disubstituted furans possessing 4-hydroxy-3-nitrophenyl substituent.

Experimental Section

General: All reagents and solvents were commercial grade and purified prior to use when necessary. Methanol was distilled from CaH_2 under N_2 immediately before use. Thin layer chromatography (TLC) was performed using plastic-backed silica gel (225 µm) plates and flash chromatography utilized 230–400 mesh silica gel from Sigma-Aldrich. Products were visualized by UV light, and/or the use of ceric ammonium molybdate, *p*-anisaldehyde, and potassium iodoplatinate solutions. IR spectra were recorded on a Nicolet™ iS™5 FT-IR Spectrometer and are reported in wavenumbers (cm^{-1}). Liquids and oils were analyzed as neat films on a NaCl plate (transmission), whereas solids were applied to a diamond plate (ATR). Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker Ascend™ 400 (400 MHz). Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.1 ($CDCl_3$). HRMS FAB data was collected from a JEOL MStation [JMS-700] Mass Spectrometer at the University of Missouri-St Louis. A Biotage Initiator+ microwave synthesizer was used for irradiation studies. 2-Allyl-6-nitrophenol was prepared from 2-nitrophenol at 175°C.[15,16]

General procedure for Passerini-Smiles reactions (Compounds 1a-2g). To a solution of substituted 2-nitrophenol (0.2 mmol, 1 equiv) in 0.50 mL acetonitrile, aldehyde (0.26 mmol, 1.3 equiv), cyclohexyl isocyanide (0.3 mmol, 1.5 equiv), and i-Pr_2NEt (10 mol%) were added. The reaction was stirred for 72 h at 80 °C. Product was isolated via flash chromatography on silica gel, to afford compounds **1a-2g** (7- 77%).

1a: 51.3 mg, 74%; R_f = 0.50 (50:50 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* 8.2 Hz, 1H), 7.56-7.51 (m, 2H), 7.41 (d, *J* 1.0 Hz, 1H), 7.22 (d, *J* 8.3 Hz, 1H), 7.12-7.08 (m, 1H), 6.52 (d, *J* 3.1 Hz, 1H), 6.36 (dd, *J* 3.1, 1.7 Hz, 1H), 5.76 (s, 1H), 3.85-3.83 (m, 1H), 2.03-1.89 (m, 1H), 1.78-1.66 (m, 2H), 1.62-1.59 (m, 1H), 1.43-1.31 (m, 4H), 1.28-1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 150.4, 148.4, 143.8, 139.6, 135.2, 126.7, 122.2, 116.3, 111.3, 111.0, 74.8, 48.5, 32.8, 25.2; IR: (diamond plate: [cm^{-1}]): 3386 (m) [N-H], 2930 (m) [C-H], 1585 (m) [C=O], 1247 (s) [C-N]; HR-FAB MS $[M+Na]^+$ calcd for $C_{18}H_{20}N_2O_5Na^+$ 367.12644; found 367.12698.

1b: 178.7 mg, 52%; R_f = 0.50 (50:50 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* 1.4 Hz, 1H), 7.57 (s, 1H), 7.51 (dd, *J* 15.9, 7.8Hz, 1H) 7.38-7.36 (m, 2H), 7.12-7.07 (m, 2H), 6.47 (d, *J* 1.0 Hz, 1H), 5.68 (s, 1H), 3.81-3.74 (m, 1H) 1.91-1.86 (m, 2H), 1.72-1.69 (m, 2H), 1.61-1.58 (m, 1H), 1.40-1.31 (m, 3H), 1.30-1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 150.4, 143.9, 141.0, 139.5, 135.1, 126.6, 121.9, 120.9, 116.0, 108.7, 74.9, 48.3, 32.8, 32.7, 25.5, 24.7; IR: (diamond plate: [cm^{-1}]): 3389 (m) [N-H], 2931 (m) [C-H], 1585 (s) [C=O], 1248 (m) [C-N]; HR-FAB MS $[M+Na]^+$ calcd for $C_{18}H_{20}N_2O_5Na^+$ 367.12644; found 367.12698.

1c: 101.2 mg, 50%; R_f = 0.30 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.54 (br s, NH, 1H), 7.37 (d, *J* 1.0 Hz, 1H), 7.30 (d, *J* 8.5 Hz, 1H), 7.06 (d, *J* 8.6 Hz, 1H), 6.48 (d, *J* 3.0 Hz, 1H), 6.32 (d, *J* 2.72, 1H), 5.69 (s, 1H), 3.82-3.80 (m, 1H), 2.30 (s, 3H), 1.96-1.86 (m, 3H), 1.72-1.56 (m, 4H), 1.35-1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 148.5, 148.2, 143.7, 135.7, 132.3, 126.5, 116.4, 111.1, 110.8, 74.9, 48.4, 32.8, 31.0, 25.5, 24.7, 20.3; IR: (diamond plate: [cm^{-1}]): 3387 (m) [N-H], 2930 (m) [C-H], 1526 (s) [C=O], 1251 (s) [C-N]; HR-FAB MS $[M+Na]^+$ calcd for $C_{19}H_{22}N_2O_4Na^+$ 381.14209; found 381.14264.

1d: 65.3 mg, 31%; R_f = 0.41 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (br s, NH, 1H), 7.44 (d, *J* 2.1 Hz, 1H), 7.38 (s, 1H), 7.09-7.04 (m, 2H), 6.46 (d, *J* 3.0 Hz, 1H), 6.33 (dd, *J* 3.0, 1.7 Hz, 1H), 5.62 (s, 1H), 3.83-3.76 (m, 4H), 2.01-1.88 (m, 3H), 1.73-1.57 (m, 4H), 1.36-1.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 154.3, 148.7, 144.5, 143.8, 140.0, 121.7, 118.7, 111.3, 110.9, 110.4, 75.7, 56.2, 48.4, 32.8, 25.6, 24.8; IR: (diamond plate: [cm^{-1}]): 3388 (m) [N-H], 2930 (m) [C-H], 1524 (s) [C=O], 1218 (s) [C-N]; HR-FAB MS $[M+Na]^+$ calcd for $C_{19}H_{22}N_2O_6Na^+$ 397.13701; found 397.13754.

1e: 216.0 mg, 60%; R_f = 0.33 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.69 (m, 1H), 7.46 (br s, NH, 1H), 7.40 (s, 1H), 7.30-7.25 (m, 1H), 7.26-7.19 (m, 1H), 6.52 (d, *J* 3.0 Hz, 1H), 6.35 (d, *J* 2.9 Hz, 1H), 5.72 (s, 1H), 3.86-3.84 (m, 1H), 2.00-1.99 (m, 2H), 1.75-1.72 (m, 2H), 1.63-1.60 (m, 1H), 1.38-1.22 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 157.4, 154.9, 148.1, 146.8, 143.6, 139.4, 122.0, 118.3, 113.6, 110.6, 75.4, 48.3, 32.7, 32.6, 26.0, 25.5, 24.6IR: (diamond plate: [cm^{-1}]): 3393 (m) [N-H], 2931 (m) [C-H], 1526 (s) [C=O], 1266 (s) [C-N].

1f: 165.3.0 mg, 77%; R_f = 0.60 (50:50 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* 8.7 Hz, 1H), 7.51 (br d, *J* 7.5 Hz, 1H, NH), 7.47-7.40 (m, 2H), 7.25 (dd, *J* 8.7, 1.7 Hz, 1H), 6.57 (d, *J* 2.9 Hz, 1H), 6.42-6.37 (m, 1H), 5.76 (s, 1H), 3.93-3.79 (m, 1H), 2.07-1.87 (m, 2H), 1.84-1.69 (m, 2H), 1.67-1.57 (m, 1H), 1.46-1.20 (m, 5H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 150.7, 147.7, 143.9, 138.3, 129.4, 127.6, 125.3, 119.9, 111.7, 110.9, 75.0, 48.4, 32.7, 32.6, 25.4, 24.6 (2C).

1g: 276.2 mg, 64%; R_f = 0.53 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* 8.0 Hz, 1H), 7.56 (m, 2H), 7.41 (s, 1H), 7.17-7.11 (m, 1H), 6.58 (s, 1H), 5.71 (s, 1H), 3.84-3.82 (m, 1H), 1.99-1.88 (m, 2H), 1.75-1.59 (m, 4H), 1.40-1.22 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 150.2, 149.5, 142.0, 139.6, 135.3, 126.8, 122.5, 116.1, 114.3, 100.7, 74.4, 48.6, 32.9, 25.5, 24.8; IR: (diamond plate: [cm^{-1}]): 3382 (m) [N-H], 2930 (m) [C-H],

1585 (s) [C=O], 1247 (s) [C-N], 735 (w) [C-Br]; HR-FAB MS $[M+Na]^+$ calcd for $C_{18}H_{19}BrN_2O_5Na^+$ 445.03696; found 445.0315.

1h: 108.5 mg, 31%, R_f = 0.33 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* 8.2 Hz, 1H), 7.57 (m, 2H), 7.21 (d, *J* 8.4 Hz, 1H), 7.14 (dd, *J* 9.2, 6.4 Hz, 1H), 6.52 (d, *J* 3.2 Hz, 1H), 6.16 (d, *J* 3.3 Hz, 1H), 5.68 (s, 1H), 3.85-3.83 (m, 1H), 2.01-1.89 (m, 2H), 1.79-1.60 (m, 4H), 1.42-1.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 150.3, 148.0, 139.7, 138.1, 135.2, 126.8, 122.4, 116.2, 113.7, 107.7, 74.6, 48.7, 32.8, 25.6, 24.8; IR: (diamond plate: [cm^{-1}]): 3386 (m) [N-H], 2931 (m) [C-H], 1585 (s) [C=O], 1247 (s) [C-N], 740 (w) [C-Cl].

1i and **2b** (Partially inseparable mixture : 105.8 mg, 25%), **1i :** R_f = 0.41 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* 8.2 Hz, 1H), 7.59-7.55 (m, 2H), 7.20 (d, *J* 8.2 Hz, 1H), 7.13 (dd, *J* 7.4, 7.4 Hz, 1H) 6.52 (d, *J* 3.3 Hz, 1H), 6.4 (d, *J* 3.3 Hz, 1H), 5.73 (s, 1H), 3.85-3.83 (m, 1H), 2.00-1.88 (m, 2H), 1.79-1.72 (m, 3H), 1.62-1.60 (m, 2H), 1.41-1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 153.9, 150.3, 139.7, 135.2, 126.7, 122.4, 121.6, 116.3, 114.1, 89.9, 74.4, 48.6, 32.9, 32.7, 25.6, 24.8. Compound **2b** observed as inseparable mixture of **1i** and **2b**. **2b:** R_f = 0.51 (40:60 EtOAc:Hex).

1j and **2c** (Partially inseparable mixture : 186.3 mg, 18%), **1j:** R_f = 0.41 (40:60 EtOAc:Hex); **2c**: R_f = 0.78 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.03 (s, 1H), 7.59 (d, *J* 8.7 Hz, 1H), 7.11 (d, *J* 8.7, 1H), 6.06 (d, *J* 2.8 Hz, 1H), 5.92 (d, *J* 2.6 Hz, 1H), 5.79 (br s, NH, 1H), 4.77 (s, 1H), 3.82-3.75 (m, 1H), 2.26 (s, 3H), 1.93-1.84 (m, 2H), 1.66-1.57 (m, 3H), 1.40-1.29 (m, 2H), 1.19-1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 154.6, 153.0, 149.6, 138.3, 133.5, 130.2, 124.8, 120.3, 109.9, 106.8, 52.0, 48.8, 33.0, 25.6, 24.8, 13.8. **2c** HR-FAB MS $[M+H]^+$ calcd for $C_{19}H_{23}N_2O_4^+$ 359.1605; found 359.16071.

2d: 103.2 mg, 27%, R_f = 0.74 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.03 (s, 1H), 7.58 (d, *J* 8.7 Hz, 1H), 7.10 (d, *J* 8.7 Hz, 1H), 5.94 (s, 1H), 5.86 (br s, NH, 1H), 4.72 (s, 1H), 3.78-3.77 (m, 1H), 2.15 (s, 3H), 2.04-1.89 (m, 5H), 1.84-1.66 (m, 3H), 1.65-1.39 (m, 2H), 1.37-1.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 154.5, 148.2, 138.2, 133.4, 130.4, 124.8, 120.2, 115.2, 112.4, 51.9, 48.8, 33.0, 32.8, 25.6, 24.8, 11.5, 10.0.

1k: 16.1 mg, 7%; R_f = 0.56 (33:67 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* 8.8 Hz, 1H), 7.50 (br d, *J* 8.0 Hz, NH, 1H), 7.39 (d, *J* 1.8 Hz, 1H), 7.29 (dd, *J* 8.7, 1.8 Hz, 1H), 6.58 (d, *J* 3.4 Hz, 1H), 6.19 (d, *J* 3.4 Hz, 1H), 5.68 (s, 1H), 3.91-3.81 (m, 1H), 2.05-1.98 (m, 1H), 1.96-1.89 (m, 1H), 1.83-1.71 (m, 2H), 1.67-1.58 (m, 1H), 1.44-1.22 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 150.6, 147.2, 138.4, 138.3, 129.5, 127.7, 125.6, 119.7, 114.1, 107.1, 74.7, 48.6, 32.7, 32.6, 25.4, 24.6 (2C).

1l and **2e :** Inseparable mixture of compounds **1l** and **2e** (47.1 mg, 17%)**. 1l:** R_f = 0.56 (33:67 EtOAc:Hex). **2e:** R_f = 0.50 (33:67 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.05 (s, 1H), 7.48 (s, 1H), 6.57 (d, *J* 3.2 Hz, 1H), 6.27 (d, *J* 3.5 Hz, 1H), 5.87 (d, *J* 3.5 Hz, 1H), 5.25 (s, 1H), 3.87-3.77 (m, 1H), 2.00-1.86 (m, 2H), 1.77-1.70 (m, 4H), 1.43-1.31 (m, 2H), 1.24-1.13 (m, 2H).

1m and **2f :** (128.0 mg, 58%). Compound **1m** observed as inseparable mixture of **1m** and **2f. 1m:** R_f = 0.40 (33:67 EtOAc:Hex), **2f**: R_f = 0.38 (33:67 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.06 (s, 1H), 7.45 (s, 1H), 6.15 (d, *J* 3.1 Hz, 1H), 5.97 (dd, *J* 3.0, 0.9 Hz, 1H), 5.67 (br d, *J* 7.6 Hz, NH, 1H), 5.18 (s, 1H), 3.88-3.78 (m, 1H), 2.27 (s, 3H), 1.99-1.86 (m, 2H), 1.73-1.57 (m, 4H), 1.39-1.31 (m, 2H), 1.21-1.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 153.8, 153.0, 134.4, 130.9, 130.1, 128.8, 126.0, 123.9, 110.4, 106.8, 68.2, 51.5, 48.7, 32.7, 29.7, 25.4, 24.6, 13.6.

2g : 54.0 mg, 26%; R_f = 0.58 (33:67 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.07 (s, 1H), 7.43 (s, 1H), 6.01 (s, 1H), 5.65 (br s, NH, 1H), 5.12 (s, 1H), 3.87-3.77 (m, 1H), 2.17 (s, 3H), 1.91 (s, 3H), 1.74-1.56 (m, 5H), 1.44-1.32 (m, 3H), 1.21-1.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 153.8, 148.2, 147.0, 134.4, 133.0, 130.2, 126.0, 123.8, 115.2, 112.8, 51.5, 48.8, 32.81, 32.76, 29.7, 25.5, 24.7, 11.4, 9.9.

1n and **3**. To a solution of 2-allyl-6-nitrophenol (86.5 mg, 0.48 mmol) in methanol (0.50 mL), 2-furaldehyde (40.0 µL, 0.48 mmol) and cyclohexyl isocyanide (60.5 µL, 0.49 mmol) were added. The reaction was stirred for 48 h at 65°C. Product was isolated via flash chromatography (SiO_2, 20% ethyl acetate in hexanes) to afford compounds **1n** (12.9 mg, 7%) and **3** (29.5 mg, 16%). Under alternate conditions (50°C for 48h), to afford compounds **1n** (48.0 mg, 26%) and **3** (5.6 mg, 3%). **1n:** R_f = 0.51 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* 8.1 Hz, 1H), 7.41 (d, *J* 7.7 Hz, 1H), 7.32 (s, 1H), 7.20-7.14 (m, 2H), 6.23 (s, 2H), 5.90-5.78 (m, 1H), 5.43 (s, 1H), 5.16 (d, *J* 10.0 Hz, 1H), 5.08 (d, *J* 17.0 Hz, 1H), 4.00-3.90 (m, 1H), 3.34 (dd, *J* 16.0, 6.7 Hz, 1H), 3.17 (dd, *J* 16.0, 6.0 Hz, 1H), 2.09-2.02 (m, 2H), 1.84-1.76 (m, 2H), 1.69-1.62 (m, 1H), 1.50-1.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 146.9, 144.7, 144.0, 143.3, 136.7, 135.4, 135.0, 124.7, 123.8, 119.5, 117.6, 108.9, 77.8, 48.2, 34.0, 33.0, 32.8, 25.5, 24.7 (2C).

3 (Conversion from 1n): A solution of **1n** (20.5 mg, 0.053 mmol) in 0.50 mL methanol was submitted to microwave irradiation (120°C, 40 minutes). Volatiles were removed *in vacuo* and crude reaction mixture submitted to flash chromatography (SiO_2, 20% ethyl acetate in hexanes) to afford hydroxyphenyl furan **3** (10.7 mg, 52%): R_f = 0.29 (40:60 EtOAc:Hex) ; R_f = 0.29 (40:60 EtOAc:Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.21 (d, *J* 1.9 Hz, 1H), 7.69 (s, 1H), 6.58 (d, *J* 3.2 Hz, 1H), 6.31 (d, *J* 3.1 Hz, 1H), 6.06-5.94 (m, 1H), 5.54 (br s, NH, 1H), 5.17 (s, 1H), 5.14 (d, *J* 4.6 Hz, 1H), 3.84-3.74 (m, 1H), 3.64 (s, 2H), 3.51 (d, *J* 6.4 Hz, 2H), 1.94-1.85 (m, 2H), 1.70-1.53 (m, 4H), 1.41-1.28 (m, 2H), 1.16-1.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 152.5, 151.3, 149.2, 134.8, 132.6, 132.1, 128.8, 122.9, 117.4, 117.2, 110.7, 106.6, 48.5, 36.7, 33.8, 32.9, 29.7, 25.5, 24.9, 19.2.

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Supplementary Material

Detailed experimental procedures and ^{1}H NMR and ^{13}C NMR spectra associated with compounds reported in this article are available as supplementary information.

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