SUPPORTING INFORMATION

Supported *p*-Toluenesulfonic Acid as a Highly Robust and Eco-Friendly Isocyanide Scavenger

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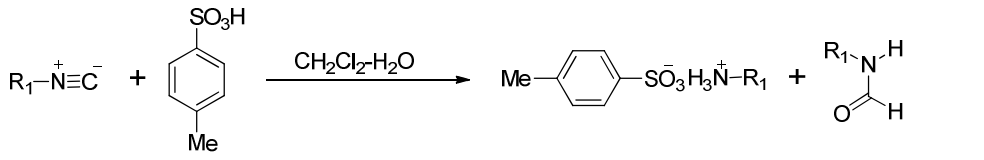
General Information. Commercially available starting materials and reagents were purchased and used without further purification from freshly opened containers. Polymer-immobilized *p*-toluenesulfonic acids employed in this study were purchased from different commercial sources. Polystyrene-supported *p*-toluenesulfonic acid (PS–*p*-TsOH) was purchased from Aldrich [reference number: 532312 (2.6 mmol/g), €1.90/mmol] and silica-immobilized p-toluenesulfonic acid (Si–*p*-TsOH) was purchased from SiliCycle [reference number: R60530B (0.59 mmol/g), €18.80/mmol]. All solvents were purified and dried by standard methods. Organic extracts were dried with anhydrous Na_2SO_4. The reactions were monitored by TLC with 2.5 mm Merck silica gel GF 254 strips and purified compounds each showed a single spot. Unless stated otherwise, UV light and/or iodine vapour were used for the detection of compounds. The synthesis and purification of all compounds were accomplished using the equipment routinely available in organic chemistry laboratories for parallel synthesis. Most of the preparative experiments were performed in coated Kimble vials on a PLS (6×4) Organic Synthesiser with orbital stirring. Purification of isolated products was carried out by column chromatography or by using an ISCO Combiflash system that employs pre-packed silica gel columns. Compounds were routinely characterised by spectroscopic and analytical data. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer 1640 FTIR spectrophotometer with samples as potassium bromide pellets, only noteworthy IR absortions are listed (cm^{-1}). The NMR spectra were recorded on Bruker AM300 MHz (^1H) and 75 MHz (^{13}C) and XM500 spectrometers. Chemical shifts are given as δ values against tetramethylsilane as internal standard and *J* values are given in Hz. Mass spectra were obtained on a Varian MAT-711 instrument. High-resolution mass spectra (HRMS) were obtained on an Autospec Micromass spectrometer.

Representative procedure for the reaction of isocyanides 1 with *p*-TsOH in CH_2Cl_2/H_2O[1]



1a) R_1 = Bn
1b) R_1 = Cy
1c) R_1 = *t*-Bu

2

4a) R_1 = Bn, 69%
4b) R_1 = Cy, 72%
4c) R_1 = *t*-Bu, 59%

5a) R_1 = Bn, 18 %
5b) R_1 = Cy, 22%
5c) R_1 = *t*-Bu, 15%

To a solution of *p*-toluenesulfonic acid (1 mmol) in a 10:1 CH_2Cl_2/H_2O mixture (5 mL) was added the corresponding isocyanide (**1a-c**) (1 mmol). The reaction mixture was submitted to orbital stirring at room temperature until reactions reached completion (30–60 min) as indicated by TLC. Evaporation of the solvent afforded a residue, which was purified by chromatographic methods on silica gel using dichloromethane/methanol mixtures as eluent.

Phenylmethanaminium 4-methylbenzenesulfonate (**4a**): Mp 176-178 ºC (MeOH). Lit (177-180 ºC).[2] IR (KBr) (νmax cm^{-1}): 3113, 3023, 2919, 1624, 1487, 1448, 1393.^{1}H-NMR (250 MHz, DMSO-d_6): δ 2.28 (3H, s, CH_3), 4.02 (2H, s, CH_2), 7.09–7.12 (2H, d, *J* = 8.0 Hz, Aromatics), 7.36–7.49 (7H, m, Aromatics), 8.15 (3H, brs, NH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 20.9, 42.5, 125.7, 128.5, 128.7, 129.0, 129.2, 134.0, 138.6, 144.7.

Cyclohexylammonium 4-methylbenzenesulfonate (**4b**): Mp 174-176 ºC (MeOH) Lit (181-182 ºC)[2]. IR (KBr) (νmax cm^{-1}): 3048, 2939, 2861, 1601, 1534, 1451. ^{1}H-NMR (250 MHz, DMSO-d_6): δ 1.06–1.86 (10H, m, Cy), 2.28 (3H, s, CH_3), 2.51 (1H, m, Cy), 7.10–7.14 (2H, d, *J* = 7.9 Hz, Aromatics), 7.47–7.50 (2H, d, *J* = 7.9 Hz, Aromatics), 7.73 (3H, brs, NH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 20.9, 23.8, 24.6, 30.3, 49.5, 125.6, 128.4, 138.3, 145.0.

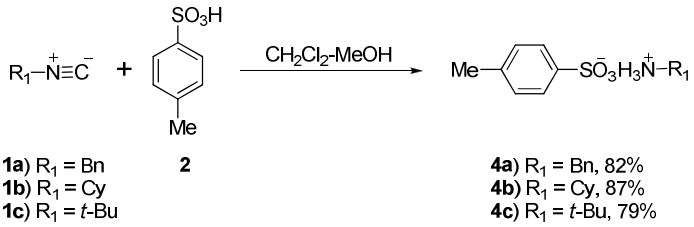
2-Methylpropan-2-aminium 4-methylbenzenesulfonate (**4c**): Mp 215-217 ºC (MeOH) Lit (220-222 ºC)[2]. IR (KBr) (νmax cm^{-1}): 3029, 2970, 2920, 2824, 2618, 1627, 1524, 1494, 1479, 1402. ^{1}H-NMR (250 MHz, DMSO-d_6): δ 1.22 (9H, m, $C(CH_3)_3$), 2.28 (3H, s, CH_3), 7.10–7.13 (2H, d, *J* = 7.8 Hz, Aromatics), 7.47–7.50 (2H, d, *J* = 7.8 Hz, Aromatics), 7.76 (3H, brs, NH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 20.9, 27.2, 51.2, 125.6, 128.4, 138.3, 145.1.

N-Benzylformamide (**5a**): Mp 59-60 ºC (MeOH). Lit (62-63 ºC).[2] IR (KBr) (νmax cm^{-1}): 3269, 1650, 1637, 1531, 1497, 1454, 1387. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 4.28–4.38 (2H, m, CH_2), 6.10 (1H, brs, NH), 7.18–7.29 (5H, m, Aromatics), 8.13 (1H, s, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 41.9, 127.5, 127.6, 128.6, 137.5, 161.1.

N-Cyclohexylformamide (**5b**): Mp 38-40 ºC (MeOH). Lit (39.5 ºC).[2] IR (KBr) (νmax cm^{-1}): 3256, 1683, 1506. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.88–1.80 (10H, m, Cy), 3.60 (1H, m, CH), 6.52 (1H, brs, NH), 7.87 (1H, s, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.4, 25.2, 32.7, 46.9, 160.5

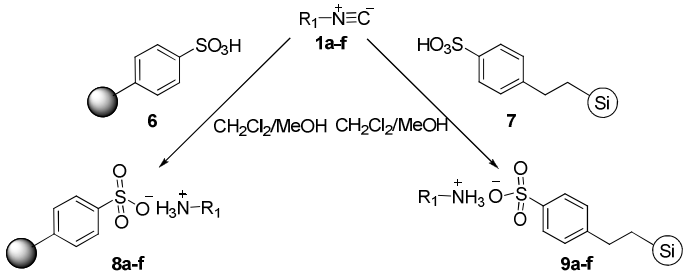
N-*tert*butylformamide (**5c**): yellow oil. Lit (16 ºC).[2] IR (KBr) (νmax cm^{-1}): 3295, 1688. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.22 (9H, m, $C(CH_3)_3$), 6.41 (1H, brs, NH), 8.17 (1H, s, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 30.8, 50.9, 160.4.

Representative procedure for the hydrolytic quenching of isocyanides 1 with *p*-TsOH in CH_2Cl_2/MeOH



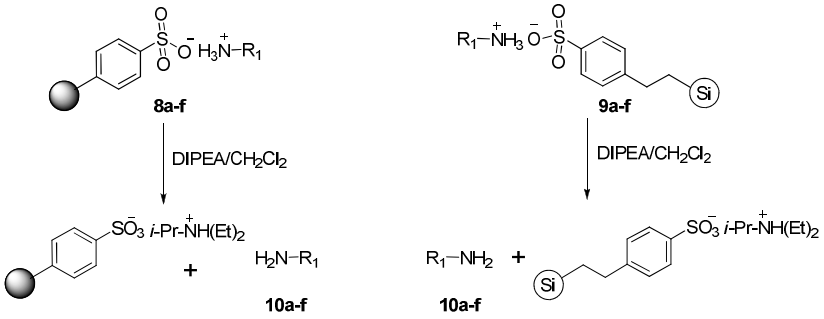
To a Kimble vial containing a solution of *p*-toluenesulfonic acid (1 mmol) in a 3:1 CH_2Cl_2/MeOH mixture (5 mL) was added the corresponding isocyanide (**1a-c**) (0.8 mmol). The reaction mixture was submitted to orbital stirring at room temperature until reactions reached completion (30–60 min) as indicated by TLC. Evaporation of the solvent afforded a residue, which was purified by chromatographic methods on silica gel using dichloromethane/methanol mixtures as eluent. Pure samples isolated exhibited analytical and spectroscopical data identical to those above described.

Representative procedure for the hydrolytic quenching of isocyanides 1 employing supported *p*-TsOH



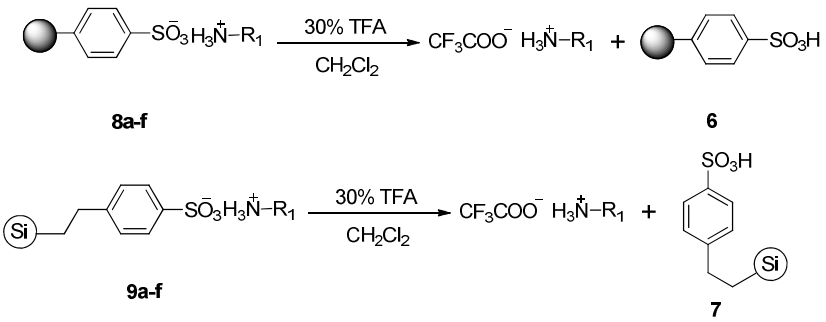
To a Kimble vial containing 2.0 mmol of the supported *p*-toluenesulfonic acid (PS-*p*-TsOH or Si-*p*-TsOH TsOH) in a 3:1 CH_2Cl_2/MeOH mixture (5 mL) was added the corresponding isocyanide **1** (1.0 mmol). The reaction mixture was submitted to orbital stirring at room temperature until the reactions reached completion (30–60 min). The polymer-supported salt was filtered off and successively washed with the proper solvent.

Representative procedure for amine synthesis employing PS-*p*-TsOH under the catch and release sequence



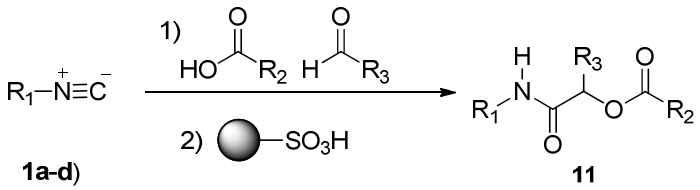
The recovered polymer-supported salt **8** or **9** (0.20 g) was added to a Kimble vial containing 6 mL of a solution of *N*,*N*-Diisopropylethylamine (2.0 mmol) in CH_2Cl_2. The reaction mixture was submitted to orbital stirring at room temperature for 2 h. The polymeric material was filtered off and washed [3 times (10 mL)] with MeOH, AcOEt and CH_2Cl_2. The solvent was removed from the filtrates under vacuum to give an oily residue containing the amine **10**.

Representative procedure for the regeneration of the polymer-supported *p*-toluenesulfonic acids (6 and 7).



The corresponding recovered polymer-supported salt (**8** or **9)** (0.20 g) was added to a Kimble vial containing 5 mL of a solution of 30% of trifluoroacetic acid in CH_2Cl_2. The reaction mixture was submitted to orbital stirring at room temperature for 2 h. The polymeric material was filtered off and successively washed [3 times (10 mL)] with MeOH, AcOEt and CH_2Cl_2 and dried under vacuum for 12 h at room temperature.

Representative procedure for the Passerini reaction employing PS-*p*-TsOH as an isocyanide scavenger[4]



To a Kimble vial containing a mixture of the aldehyde (1.0 mmol) and the carboxylic acid (1.0 mmol) was added the isocyanide (1.0 mmol). The reaction mixture was submitted to orbital stirring at room temperature for 48 h. After completion of the reaction, 5 mL of a 3:1 CH_2Cl_2/MeOH mixture and PS-*p*-TsOH (2.0 mmol) and were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of the unreacted isocyanide (30–60 min). The polystyrene-supported salt was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvent from the filtrate afforded a residue, which was purified by silica gel column chromatography.

(Benzylcarbamoyl)(4-chlorophenyl)methyl benzoate (**11a**): White powder (77%). Mp: 160-162ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1167, 1250, 1551, 1656, 1716 and 3286. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.20-4.58 (2H, dd, *J* = 14.5, 7.9 Hz, CH_2), 6.24 (1H, s, CH), 6.41 (1H, brs, NH), 7.01-7.64 (12H, m, Aromatics), 7.86-8.02 (2H, d, *J* = 7.3 Hz, Aromatics).

(Cyclohexylcarbamoyl)(4-chlorophenyl)methyl benzoate (**11b**): White powder (73%). Mp: 209-211 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1116, 1263, 1561, 1653, 1724 and 3272. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.08-1.92 (10H, m, Cy), 3.76-3.89 (1H, m, CH), 6.05-6.08 (1H, d, *J* = 7.4 Hz, NH), 6.26 (1H, s, CH), 7.34-7.37 (2H, *J*= 8.4 Hz,

Aromatics), 7.45-7.65 (5H, m, Aromatics), 8.06-8.09 (2H, d, *J*= 7.4 Hz, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.5, 25.2, 32.7, 48.2, 75.0, 128.6, 128.7, 128.8, 129.6, 133.0, 133.6, 134.2, 134.7, 164.6, 166.8.

(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl benzoate (**11c**): White powder (55%). Mp: 199-201 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1116, 1258, 1556, 1652, 1722 and 3280. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.37 (9H, s, $3CH_3$), 6.04 (1H, s, NH), 6.18 (1H, s, CH), 7.34-7.37 (2H, d, *J*= 8.4 Hz, Aromatics), 7.43-7.69 (5H, m, Aromatics), 7.98-8.18 (2H, d, *J*= 8.4 Hz, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.5, 51.5, 75.1, 128.6, 128.7, 128.8, 129.6, 133.0, 133.6, 134.3, 134.7, 164.6, 166.8.

1-(benzylcarbamoyl)ethyl acetate (**11d**): White powder (67%). Mp: 83-84 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1237, 1557, 1654, 1733 and 3277. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.32-1.35 (3H, d, *J*= 6.8 Hz, CH_3), 1.95 (3H, s, CH_3), 4.30-4.32 (2H, d, *J*= 5.8 Hz, CH_2), 5.07-5.10 (1H, m, CH), 6.24 (1H, brs, NH), 7.09-7.20 (5H, m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.8, 20.9, 42.9, 70.5, 126.3, 127.4, 128.6, 137.7, 169.4, 170.2.

1-(Cyclohexylcarbamoyl)ethyl acetate (**11e**): White powder (94%). Mp: 81-82 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1231, 1560, 1652, 1743 and 3276. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.02-1.92 (13H, m, CH_3 + Cy), 2.14 (3H, s, CH_3), 3.78 (1H, m, CH), 5.12-5.18 (1H, m, CH), 5.91 (1H, brs, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.7, 20.9, 24.6, 25.3, 32.8, 47.7, 70.5, 169.1, 169.3.

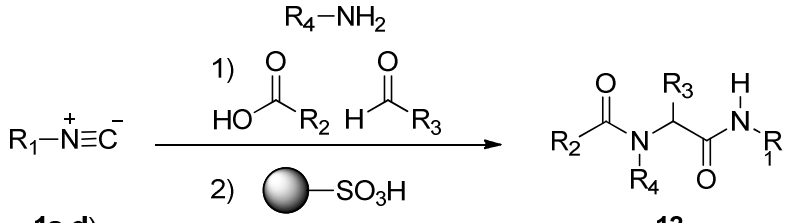
1-(*tert*-butylcarbamoyl)ethyl acetate (**11f**): White powder (73%). Mp: 85-87 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1222, 1559, 1653, 1739 and 3277. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.35 (9H, s, $3CH_3$), 1.40-1.45 (3H, d, *J*= 6.8 Hz, CH_3), 2.13 (3H, s, CH_3), 4.98-5.15 (1H, q, *J*= 6.8 Hz, CH), 5.86 (1H, brs, NH).

1-(benzylcarbamoyl)ethyl benzoate (**11g**): White powder (81%). Mp: 72-74 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1114, 1221, 1542, 1662, 1720, 1749 and 3263. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.61-1.63 (3H, d, J= 6.7 Hz, CH_3), 4.00-4.18 (2H, m, CH_2), 5.48-5.55 (1H, m, CH), 6.76 (1H, brs, NH), 7.26-7.64 (8H, m, Aromatics), 8.07-8.10 (2H, d, J= 7.7 Hz, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.6, 40.8, 70.7, 128.4, 128.5, 128.7, 129.1, 129.5, 129.8, 133.5, 165.0, 169.9, 170.6

1-(Cyclohexylcarbamoyl)ethyl benzoate (**11h**): White powder (74%). Mp: 125-127 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1177, 1274, 1556, 1649, 1717 and 3266. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.05-1.95 (13H, m, CH_3CH + Cy), 3.75-3.85 (1H, m, CH), 5.40-5.47 (1H, q, *J*= 6.7 Hz, CH), 6.00-6.02 (1H, d, *J*= 6.0 Hz, NH), 7.46-7.64 (3H, m, Aromatics), 8.04-8.10 (2H, m, Aromatics).

1-(*tert*-butylcarbamoyl)ethyl benzoate (**11i**): White powder (82%). Mp: 164-166 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1119, 1263, 1560, 1660, 1719 and 3292. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s, $3CH_3$), 1.55-1.57 (3H, d, *J*= 6.7 Hz, CH_3), 5.32-5.36 (1H, d, *J*= 6.7 Hz, CH), 5.98 (1H, brs, NH), 7.45-7.64 (3H, m, Aromatics), 8.04-8.06 (2H, d, *J*= 7.7 Hz, Aromatics).

Representative procedure for the Ugi reaction employing PS-*p*-TsOH as an isocyanide scavenger[5]



In a Kimble vial a mixture of the aldehyde (1.0 mmol) and the amine (1.0 mmol) in MeOH (2 mL) was prepared. The reaction mixture was submitted to orbital stirring at room temperature for 1 h. After this time, the carboxylic acid (1.0 mmol) and the isocyanide (1.0 mmol) were added. The reaction mixture was submitted to orbital stirring at room temperature for 48 h. After completion of the reaction, PS-*p*-TsOH (2.0 mmol) and CH_2Cl_2 (3 mL) were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of the unreacted isocyanide (30–60 min). The polystyrene-supported salt was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a residue, which was purified by chromatographic methods on silica gel.

***N*-[(benzylcarbamoyl)(4-chlorophenyl)methyl]-N-phenylbenzamide** (**12a**): White powder (81%). Mp: 194-196 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1239, 1341, 1489, 1551, 1641, 3246. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.53-4.55 (2H, d, *J*= 5.7 Hz, CH_2), 6.15 (1H,s, CH), 6.37 (1H, brs, NH), 6.94-7.35 (19H, m, Aromatics).

***N*-[(Cyclohexylcarbamoyl)(4-chlorophenyl)methyl]-N-phenylbenzamide** (**12b**): White powder (63%). Mp: 214-216 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1236, 1342, 1569, 1643, 3259. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.07-1.99 (10H, m, Cy), 3.85-3.88 (1H, m, CH), 5.89-5.91 (1H, d, *J*= 7.6 Hz, NH), 6.13 (1H, s, CH), 6.98-7.31 (14H,

m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.6, 25.3, 32.6, 48.6, 65.7, 127.2, 127.5, 128.3, 128.4, 128.5, 129.4, 130.0, 131.3, 133.2, 134.2, 135.6, 140.9, 168.1, 171.2.

***N*-[(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl]-N-phenylbenzamide** (**12c**): White powder (65%). Mp: 150-152ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1352, 1491, 1631, 1680, 3289. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.37 (9H, s, 3x CH_3), 5.90 (1H, brs, NH), 6.07 (1H, s, CH), 6.98-7.30 (14H, m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.5, 51.6, 66.0, 127.2, 127.5, 128.3, 128.4, 128.5, 129.4, 130.0, 131.3, 133.3, 134.2, 135.6, 140.8, 168.2, 171.0.

2-(N-phenylacetamido)-N-benzylpropanamide (**12d**): White poder (58%). Mp: 121-123 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1450, 1550, 1623, 1670, 3258. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.32-1.35 (3H, d, *J*= 6.8 Hz, CH_3), 1.94 (3H, s, CH_3), 4.29-4.32 (2H, d, *J*= 5.8 Hz, CH_2), 5.04-5.13 (1H, q, *J*= 6.8 Hz, CH), 6.23 (1H, brs, NH), 7.09-7.22 (10H, m, Aromatics).

2-(N-phenylacetamido)-N-cyclohexylpropanamide (**12e**): Yellow oil (66%). IR (KBr) (νmax cm^{-1}): 1410, 1448, 1544, 1612, 1669, 3293. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.04-1.06 (3H, d, *J*= 7.1 Hz, CH_3) 1.17-1.90 (13H, m, Cy, CH_3CO), 3.72-3.82 (1H, m, CH), 5.14-5.19 (1H, q, *J*= 7.2 Hz, CH), 6.67 (1H, m, NH), 7.07-7.60 (5H, m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.4, 20.6, 24.5, 25.3, 31.9, 48.8, 66.3, 118.7, 119.7, 129.3, 129.6, 172.1, 174.8.

2-(N-phenylacetamido)-N-*tert*-butylpropanamide (**12f**): White powder (73%). Mp: 112-114 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1416, 1445, 1548, 1612, 1671, 3299. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.99-1.02 (3H, d, *J*= 7.2 Hz, CH_3), 1.37 (9H, s, 3x CH_3), 1.84 (3H, s, CH_3), 5.12-5.14 (1H, m, CH), 6.62 (1H, brs, NH), 7.12-7.42 (5H, m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.5, 25.3, 32.6, 47.9, 66.1, 127.2, 128.4, 129.7, 135.9, 168.8, 170.5.

2-(N-benzylacetamido)-N-benzylpropanamide (**12g**): White powder (60%). Mp: 90-92 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1237, 1369, 1557, 1654, 1732, 2989, 3278. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.27-1.39 (3H, d, *J*= 6.8 Hz, CH_3), 1.94 (3H, s, CH_3), 4.06-4.39 (4H, m, 2x CH_2), 5.00-5.20 (1H, q, *J*= 6.8 Hz, CH), 6.23 (1H, brs, NH), 6.91-7.26 (10H, m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.8, 20.9, 43.0, 43.2, 70.5, 126.9, 127.2, 127.5, 127.8, 128.1, 128.6, 137.5, 137.7, 169.4, 170.25.

2-(N-benzylacetamido)-N-cyclohexylpropanamide (**12h**): Orange oil (77%). IR (KBr) (νmax cm^{-1}): 1381, 1449, 1534, 1649, 3284. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.92-1.71 (13H, m, Cy, CH_3), 1.90 (3H, s, CH_3), 3.49-3.52 (1H, m, CH), 4.43 (2H, brs, CH_2), 4.90-4.93 (1H, m, CH), 6.12 (1H, brs, NH), 6.99-7.20 (5H, m, Aromatics).

2-(N-benzylacetamido)-N-*tert*-butylpropanamide (**12i**): White powder (57%). Mp: 113-115 ºC (MeOH). IR (KBr) (νmax cm^{-1}):1224, 1362, 1467, 1555, 1622, 1671, 3268. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.20-1.24 (3H, d, *J*= 7.1 Hz, CH_3), 1.29 (9H, s, 3xCH_3), 2.08 (3H, s, CH_3), 4.60 (2H, s, CH_2), 5.01-5.08 (1H, m, CH), 6.22 (1H, brs, NH), 7.17-7.36 (5H, m, Aromatics).

N-[1-(benzylcarbamoyl)ethyl]-N-benzylbenzamide (**12j**): White powder (69%). Mp: 140-142 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1239, 1431, 1529, 1605, 1673, 3321. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.38-1.52 (3H, d, *J*= 6.7 Hz, CH_3), 4.46-5.02 (6H, m, NH, CH_2, CH_2, CH), 7.05-7.54 (15H, m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.8, 43.3, 43.5, 50.9, 126.4, 126.8, 127.2, 127.4, 127.5, 127.9, 128.4, 128.5, 129.8, 135.7, 136.1, 138.1, 170.1, 174.5.

N-[1-(*tert*-butylcarbamoyl)ethyl]-N-benzylbenzamide (**12k**): White powder (76%). Mp: 129-131 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1228, 1387, 1492, 1540, 1625, 1682, 3359. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.28 (9H, s, 3xCH_3), 1.36-1.38 (3H, d, *J*= 7.0 Hz, CH_3), 4.61 (2H, s, CH_2), 4.73-5.00 (1H, m, CH), 6.39-6.74 (1H, brs, NH), 7.12-7.46 (10H, m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.6, 28.5, 44.1, 51.0, 126.2, 126.7, 126.9, 127.2, 128.4, 128.9, 129.4, 136.0, 137.6, 169.8, 173.3.

N-[1-(benzylcarbamoyl)ethyl]-N-phenylbenzamide (**12l**): White powder (58%). Mp: 110-112 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1228, 1387, 1492, 1540, 1625, 1682, 3359. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.24-1.27 (3H, d, *J*= 7.4 Hz, CH_3), 4.38-4.48 (1H, dd, *J*= 5.5 Hz, 14.8 Hz, CH_2), 4.56-4.66 (1H, dd, *J*= 5.5 Hz, 14.7 Hz, CH_2), 5.36-5.58 (1H, q, *J*= 7.2 Hz, CH), 6.86-6.98 (2H, m, NH, Aromatics), 7.05-7.41 (14H, m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.5, 43.4, 54.4, 127.2, 127.5, 127.7, 128.0, 128.3, 128.5, 128.7, 129.4, 129.5, 135.7, 138.3, 139.2, 171.2, 171.6.

N-[1-(cyclohexylcarbamoyl)ethyl]-N-phenylbenzamide (**12m**): White powder (77%). Mp: 116-118 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1221, 1353, 1449, 1566, 1671, 3297. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.05-2.04 (10H, m, Cy), 1.20-1.23 (3H, d, *J*= 7.0

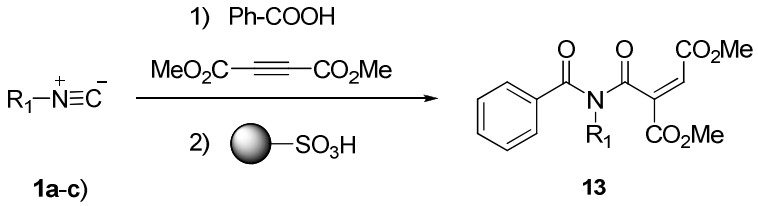
Hz, CH_3), 3.72-3.98 (1H, m, CH), 5.30-5.51 (1H, q, *J*= 7.0 Hz, CH), 6.67-6.70 (1H, d, *J*= 7.7 Hz, NH), 6.99-7.30 (10H, m, Aromatics).

N-[1-(*tert*-butylcarbamoyl)ethyl]-N-phenylbenzamide (**12n**): White powder (64%). Mp: 158-160 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1249, 1385, 1491, 1541, 1618, 1683, 3305. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.15-1.20 (3H, d, *J*= 7.1 Hz, CH_3), 1.40 (9H, s, 3xCH_3), 5.32-5.43 (1H, q, *J*= 7.1 Hz, CH), 6.66 (1H, brs, NH), 7.00-7.23 (10H, m, Aromatics).

N-[(benzylcarbamoyl)(4-chlorophenyl)methyl]-N-phenylacetamide (**12o**). White powder (61%). Mp: 192-194 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1231, 1392, 1489, 1550, 1626, 1687, 3295. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.87 (3H, s, CH_3), 4.44-4.55 (2H, d, *J*= 5.7 Hz, CH_2), 6.03 (1H, s, CH), 6.17 (1H, brs, NH), 6.98-7.45 (14H, m, Aromatics). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 23.0, 43.6, 64.1, 127.3, 127.5, 128.2, 128.4, 128.5, 129.0, 130.0, 131.6, 132.7, 134.4, 134.5, 135.2, 169.9, 172.14.

N-[(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl]-N-phenylacetamide (**12p**). White powder (73%). Mp: 201-203 ºC (MeOH). IR (KBr) (νmax cm^{-1}): 1224, 1386, 1490, 1543, 1632, 1688, 3309. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (9H, s, 3xCH_3), 1.87 (3H, s, CH_3), 5.69 (1H, brs, NH), 5.92 (1H, s, CH), 6.95-7.33 (9H, m, Aromatics).

Representative procedure for the synthesis of dimethyl (*E*)-2-{[benzoylamino]carbonyl}-2-butenedioates 13[6] employing PS-*p*-TsOH as an isocyanide scavenger



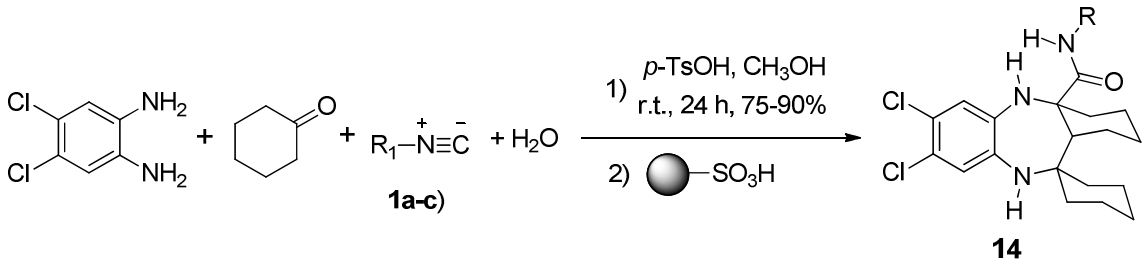
To a solution of dimethyl acetylenedicarboxylate (1.0 mmol) and benzoic acid (1.0 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise a solution of the corresponding isocyanide (1.0 mmol) in dry CH_2Cl_2 (3 mL) at room temperature over 10 min. The reaction mixture was submitted to orbital stirring for 48 h. After completion of the reaction, PS-*p*-TsOH (2.0 mmol) and MeOH (4 mL) were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of the unreacted isocyanide (30–60 min), as indicated by TLC. The polystyrene-supported salt was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a residue, which was purified by chromatographic methods on silica gel.

Dimethyl (E)-2-{[benzoyl(benzyl)amino]carbonyl}-2-butenedioate (**13a**). Yellow oil (76%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.57 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 4.50 (2H, m, CH_2), 6.52-6.53 (1H, d, *J*= 1.8 Hz, CH), 6.92-7.35 (9H, m, Aromatics), 7.96-7.93 (1H, d, *J*= 7.8 Hz, Aromatics).

Dimethyl (E)-2-{[benzoyl(cyclohexyl)amino]carbonyl}-2-butenedioate (**13b**). Yellow oil (88%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.91-2.15 (10H, m, Cy), 3.52 (1H, m, CH), 3.55 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 6.34 (1H, s, CH), 7.22-7.45 (4H, m, Aromatics), 7.89-7.92 (1H, d, *J*= 8.1 Hz, Aromatics).

Dimethyl (E)-2-{[benzoyl(tert-butyl)amino]carbonyl}-2-butenedioate (**13c**). White powder (94%). Mp: 124-126 ºC (MeOH) Lit (130-132 ºC)[6]. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.55 (9H, s, 3xCH_3), 3.59 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 6.38 (1H, s, CH), 7.35-7.38 (2H, m, Aromatics), 7.52 (1H, m, Aromatics), 7.72-7.75 (2H, d, *J*= 8.4 Hz, Aromatics).

Representative procedure for the synthesis of tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamides 14[7] employing PS-*p*-TsOH as an isocyanide scavenger



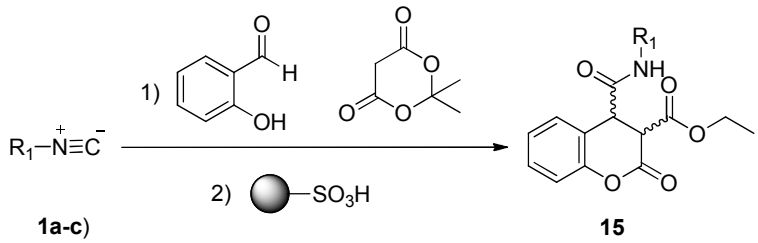
A solution of the corresponding *o*-phenylenediamine (1.0 mmol) and cyclohexanone (2.0 mmol) in methanol (5 mL) was submitted to orbital stirring for 4 h at ambient temperature. After completion of the reaction, as indicated by TLC, the corresponding isocyanide (1.0 mmol) and water (0.2 mL) were added to the reaction mixture. The resulting mixture was stirred for 20 h at ambient temperature. After completion of the reaction, PS-*p*-TsOH (2.0 mmol) and CH_2Cl_2 (4 mL) were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of unreacted isocyanide (30–60 min), as indicated by TLC. The polystyrene-supported salt was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a solid, which was purified by crystallization.

N-benzyl-7,8-dichloro-2,3,4,5-tetrahydro-2-cyclohexyl-3,4-cyclohexyl-1H-[1,5]benzodiazepine-2-carboxamide (**18a**). White powder (77%). Mp: 178-180 ºC (MeOH) Lit (193-195 ºC).[7] ^{1}H-NMR (300 MHz, DMSO): δ 1.20-1.63 (18H, m, 9 x CH_2), 2.48-2.49 (1H, m, CH), 4.47-4.49 (2H, d, *J*= 5.1 Hz, CH_2), 6.21 (1H, s, NH), 6.77 (1H, s, NH), 6.99 (1H, s, NH), 7.18-7.50 (7H, m, Aromatics).

7,8-dichloro-N-cyclohexyl-2,3,4,5-tetrahydro-2-cyclohexyl-3,4-cyclohexyl-1H-[1,5]benzodiazepine-2-carboxamide (**14b**). Orange oil (83%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.84-2.07 (28H, m, 14 x CH_2), 3.17-4.64 (5H, m, CH, CH2, 3 NH), 6.38-7.21 (2H, m, Aromatics).

N-*tert*-butyl-7,8-dichloro-2,3,4,5-tetrahydro-2-cyclohexyl-3,4-cyclohexyl-1H-[1,5]benzodiazepine-2-carboxamide (**14c**). White powder (85%). Mp: 260 ºC (MeOH) Lit (168-170 ºC) [7]. ^{1}H-NMR (300.13 MHz, DMSOd6) 1.10 (9H, s, 3 x CH_3), 1.18-1.70 (18H, m, 9 x CH_2), 2.28 (1H, t, J = 7.7 Hz, CH), 4.24 (1H, brs, NH), 5.30 (1H, brs, NH), 6.03 (1H, s, Aromatic), 6.90 (1H, s, Aromatic), 6.99 (1H, s, NH).

Representative procedure for the synthesis of 3,4-dihydrocoumarins 15[8] employing PS-*p*-TsOH as an isocyanide scavenger



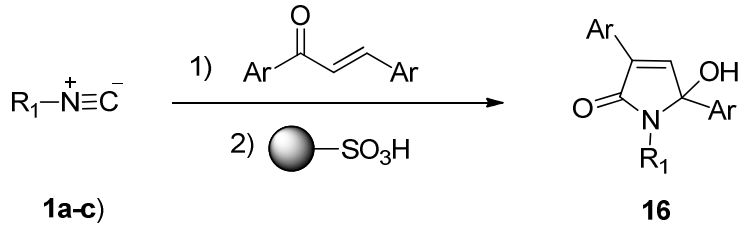
To a magnetically stirred solution of Meldrum's acid (1.0 mmol) and 2-hydroxybenzaldehyde (1.0 mmol) in ethanol (5 mL) was added the corresponding isocyanide (1.0 mmol) and the reaction mixture was submitted to orbital stirring for 8 h at room temperature. After completion the reaction, PS-*p*-TsOH (2.0 mmol) and CH_2Cl_2 (4 mL) were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of unreacted isocyanide (30–60 min), as indicated by TLC. The polystyrene-supported salt was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a solid, which was washed with cold ethanol and crystallized from *i*-PrOH.

Ethyl-4-(benzylcarbamoyl)-3,4-dihydro-2-oxo-2*H*-chromene-3-carboxylate (**15a**). White powder (79%). Mp: 134-136 ºC (MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.08-1.14 (3H, t, *J*= 7.1 Hz, CH_3), 3.77-3.79 (1H, d, *J*= 5.8 Hz, CH), 4.04-4.13 (2H, m, CH_2), 4.18-4.21 (1H, d, *J*= 5.7 Hz, CH), 4.57-4.54 (2H, CH_2), 5.66 (1H, s, NH), 6.49-6.52 (1H, d, *J*= 8.1 Hz, CH), 6.68-6.71 (1H, t, *J*= 7.4 Hz, Aromatics), 6.74-7.22 (8H, m, Aromatics).

Ethyl-4-(cyclohexylcarbamoyl)-3,4-dihydro-2-oxo-2H-chromene-3-carboxylate (**15b**). White powder (90%). Mp: 168-171 ºC (MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.86-1.69 (13H, m, Cy + CH_3), 3.52-3.60 (1H, m, CH), 3.93-4.07 (4H, m, 2 CH + CH_2), 5.57-5.60 (1H, d, *J*= 7.5 Hz, NH), 6.89-7.20 (4H, m, Aromatics).

Ethyl-4-(*tert*-butylcarbamoyl)-3,4-dihydro-2-oxo-2*H*-chromene-3-carboxylate (**15c**). White powder (84%). Mp: 181-183 ºC (MeOH) Lit (178-180 ºC)[8]. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.02-1.25 (12H, m, 3 x CH_3 + CH_3), 4.00-4.02 (1H, d, *J*= 4.8 Hz, CH), 4.05-4.20 (2H, m, CH_2), 4.25-4.26 (1H, d, *J*= 4.7 Hz, CH), 7.02-7.06 (1H, d, *J*= 8.0 Hz, Aromatics), 7.10-7.16 (1H, t, *J*= 7.4 Hz, Aromatics), 7.26-7.32 (1H, t, *J*= 7.4 Hz, Aromatics), 7.45-7.62 (1H, d, *J*= 6.5 Hz, Aromatics), 7.95 (1H, s, NH).

Representative procedure for the synthesis of 5-hydroxy-3,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones 16[9] employing PS-*p*-TsOH as an isocyanide scavenger



1a-c) **16**

A mixture containing the 1,3-diaryl-2-propen-1-one (1.0 mmol) and the corresponding isocyanide (1.0 mmol) was stirred at 150 ºC for 30 min. The reaction mixture was cooled to room temperature and the residue was dissolved in a 3:1 CH_2Cl_2/MeOH mixture (5 mL). PS-*p*-TsOH (2.0 mmol) was added and the reaction mixture was submitted to orbital stirring at room temperature until complete consumption of the unreacted isocyanide (30–60 min). The polystyrene-supported salt was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and

CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a residue, which was purified by chromatographic methods on silica gel.

1-benzyl-5-hydroxy-3,5-diphenyl-1H-pyrrol-2(5*H*)-one (**16a**). White powder (74%). Mp: 59-61 ºC (MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.19-4.29 (2H, d, *J*= 6.5 Hz, CH_2), 6.03-6.05 (1H, brs, OH), 7.04-7.20 (15H, m, Aromatics), 8.04 (1H, s, CH)

1-cyclohexyl-5-hydroxy-3,5-diphenyl-1H-pyrrol-2(5*H*)-one (**16b**). White powder (80%). Mp: 140-142 ºC (MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.80-2.06 (10H, m, Cy), 2.50 (1H, s, OH), 3.02-3.32 (1H, m, CH), 6.72 (1H, s, CH), 7.04-7.43 (8H, m, Aromatics), 7.64-7.78 (2H, m, Aromatics).

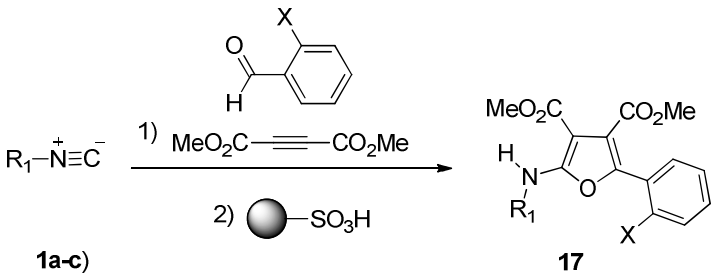
1-*tert*-butyl-3-(4-chlorophenyl)-5-hydroxy-5-phenyl-1H-pyrrol-2(5*H*)-one (**16c**). White powder (82%). Mp: 157-159 ºC (MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.24 (9H, s, 3 x CH), 2.42 (1H, s, OH), 6.62 (1H, s, CH), 7.18-7.34 (7H, m, Aromatics), 7.62-7.65 (2H, d, J= 8.5 Hz, Aromatics).

1-*tert*-butyl-5-(4-chlorophenyl)-5-hydroxy-3-phenyl-1H-pyrrol-2(5*H*)-one (**16d**). White powder (86%). Mp: 148-150 ºC (MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.25 (9H, s, 3 x CH_3), 2.52 (1H, s, OH), 6.56 (1H, s, CH), 7.09-7.23 (7H, m, Aromatics), 7.64-7.68 (2H, d, J= 8.5 Hz, Aromatics).

1-*tert*-butyl-5-hydroxy-3-(4-methoxyphenyl)-5-phenyl-1H-pyrrol-2(5*H*)-one (**16e**). Yellow oil (79%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.24 (9H, s, 3 x CH_3), 2.52 (1H, s, OH), 3.65 (3H, s, OCH_3) 6.50 (1H, s, CH), 6.67-7.09 (4H, m, Aromatics), 7.20-7.69 (5H, m, Aromatics).

1-*tert*-butyl-5-hydroxy-5-(4-methoxyphenyl)-3-phenyl-1H-pyrrol-2(5*H*)-one (**16f**). Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.25 (9H, s, 3 x CH_3), 1.87 (1H, s, OH), 3.70 (3H, s, OCH_3), 6.61-6.85 (2H, d, *J*= 6.8 Hz, Aromatics), 6.92 (1H, s, CH), 7.18-7.32 (3H, m, Aromatics), 7.41-7.61 (2H, m, Aromatics), 7.77-7.90 (2H, m, Aromatics).

Representative procedure for the synthesis of 2-aminofurans 17[10] employing PS-*p*-TsOH as an isocyanide scavenger



A mixture of the aldehyde (0.65 mmol) and dimethyl acetylenedicarboxylate (0.71 mmol) in dry benzene (6 mL) was purged with argon for 5 min. Isocyanide (0.71 mmol) was added to the above mixture by syringe and the reaction mixture was heated under reflux for 3 h. After completion of the reaction, PS-*p*-TsOH (2.0 mmol) and a 3:1 CH_2Cl_2/MeOH mixture (5 mL) were added. The reaction mixture was submitted to orbital stirring at room temperature until the unreacted isocyanide had been consumed (30–60 min). The polystyrene-supported salt was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a residue, which was purified by chromatographic methods on silica gel.

Dimethyl-2-(cyclohexylamino)-5-(2-nitrophenyl)furan-3,4-dicarboxylate (**17a**).Orange oil (80%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.22-1.99 (10H, m, Cy), 3.50 (1H, m, CH), 3.79 (6H, s, 2 x OCH_3), 6.63 (1H, d, J= 7.7 Hz, NH), 7.45-7.64 (3H, m, Aromatics), 7.85-7.88 (1H, d, J= 7.0 Hz, Aromatic).

Dimethyl-2-(benzylamino)-5-(2-chlorophenyl)furan-3,4-dicarboxylate (**17b**). Oil (61%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.43 (2H, d, J= 5.8 Hz CH_2), 3.81 (6H, s, 2 x OCH_3), 6.58 (1H, brs, NH), 7.32-7.84 (9H, m, Aromatics).

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