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A Facile Manganese Dioxide Mediated Oxidation of Primary Benzylamines to Benzamides†

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A high yielding manganese dioxide mediated oxidation of benzylamines to the corresponding amides has been developed under mild reaction conditions. The mechanism for the conversion has been explored by ^{1}H NMR spectroscopy and the role of both manganese dioxide and molecular sieves in the reaction elucidated.

Introduction

The oxidation of one functional group to another is a vital transformation in the synthesis of many pharmaceuticals, agrochemicals and natural products. So important is this conversion that a diverse range of reagents and reaction conditions have been developed to facilitate this class of reaction in an equally diverse range of substrates. The Swern oxidation and Corey-Kim modification,[1] IBX/Dess-Martin periodinane oxidations, [2,3] and ozonolysis[4] each have their place in the tool box of the synthetic organic chemist.

We have been particularly interested in manganese dioxide as an oxidising agent and the apparent capricious nature of this reagent, indeed there are numerous methods reported in the literature for the preparation[5-7] and application of manganese dioxide in organic synthesis.[7,8] However, there remains a degree of mysticism surrounding this reagent and precisely what is happening in the reaction flask.

Amides are commonly prepared by the reaction of an activated carboxylic acid derivative with an amine.[9] Alternative methods for amide synthesis include the Beckmann rearrangement[10,11] and the Schmidt reaction.[12] Unfortunately many of these methods involve hazardous reagents and produce stoichiometric quantities of noxious by-products. More recently, metal complexes have been used to access *N*-substituted amides through the dehydrogenative reaction between amines and alcohols.[13,14] The hydration of nitriles[15] and the rearrangement of aldoximes[16, 17] provide alternate synthetic routes to amides. However, avoiding the need for multiple reaction steps, activating reagents and acidic or basic media in the synthesis of amides remains an important goal in modern organic synthesis

Although the oxygenation of a carbon atom adjacent to an amine would provide the most atom efficient route to the corresponding amide, this direct conversion is difficult to achieve and has not been

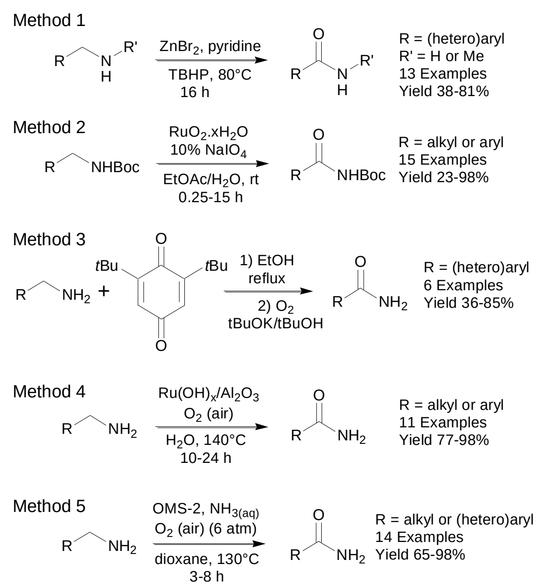


Figure 1 Methods available for the oxygenation of a carbon atom adjacent to an amine.

extensively investigated. The combination of $ZnBr_2$ and *tert*-butylhydroperoxide has been shown to convert both primary and secondary benzylamines to the corresponding amide in moderate to good yield (Method 1, Figure 1).[18]

Similarly, *in situ* generated RuO_4 has been employed as an oxidant but requires prior *tert*-butoxycarbonyl (Boc) protection of the amine (Method 2).[19] This reaction proceeds at room temperature and in excellent yield. An alternative method involves the condensation of benzylamines with 2,6-di-*tert*-butyl-*p*-benzoquinone to deliver an intermediate imine (Method 3).[20] This imine then undergoes base catalysed oxygenation to the corresponding primary amide in moderate to good yield. More recently it has been demonstrated that a diverse range of primary amines can be converted to the corresponding amide in the presence of an alumina supported ruthenium hydroxide catalyst, $Ru(OH)_x/Al_2O_3$ (Method 4).[21] Utilising a similar dehydrogenation-hydration strategy, Wang has been able to facilitate the same conversion using manganese oxide octahedral molecular sieves (OMS-2) and aqueous ammonia (Method 5).[22] This latter method, though delivering the target amides in excellent yield requires high temperatures (130°C) with reactions conducted under 6 atmospheres of air in explosion-proof Teflon apparatus.

Wang reported that using commercially sourced activated manganese dioxide yielded only 12% of the target amide compared to 83% when the OMS-2 catalyst was used. From our previous work we believed that this result may not be representative of the true activity of manganese dioxide. We therefore present a simple method for the reproducible preparation of activated manganese dioxide and the application of this reagent to the synthesis of amides from the corresponding primary amine under mild reaction conditions.

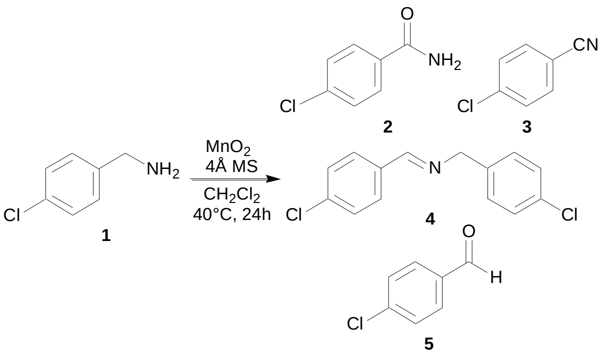
Results and Discussion

Although methods for the preparation of activated manganese dioxide are reported in the literature,[5-7] many of these methods are both time consuming and complex, with the activity of the activated catalyst varying greatly between methods but also between batches using the same method. To investigate the chemistry of manganese dioxide it is therefore necessary to establish an activation procedure that is both straightforward and reproducible. Treatment of commercially sourced activated manganese dioxide with 10% nitric acid and drying at 105°C for 48 hours yields manganese dioxide whose activity is both reproducible and independent of the initial source of manganese dioxide. When activated manganese dioxide from either Alfa Aesar or Sigma Aldrich is prepared according to our method, the product is identical in terms of activity irrespective of the initial source.

For the initial investigation 4-chlorobenzylamine **1** was selected as the starting amine as the pair of doublets in the ^{1}H NMR spectrum corresponding to *ortho*- and *meta*-hydrogens would prove diagnostic in determining product distributions should more than one product be formed in the reaction (Scheme 1).

Using reaction conditions we had developed for the oxidation of another class of substrate, namely, using air as the oxidant and heating with 25 equivalents of nitric acid washed manganese dioxide and 4Å molecular sieves in dichloromethane at 40°C for 24 hours resulted in near quantitative conversion to the corresponding amide **2** (Entry 1, Table 1).[23]

The work up for the reaction is simply to filter off the manganese dioxide using a short pad of celite and then wash the celite with hot (60°C) methanol, no further purification is required. The presence of molecular sieves was found to be essential, in their absence significant quantities of other products are observed, and a correspondingly lower yield of amide **2** is obtained (44%) (Entry 2).



Scheme 1 Oxidation of 4-chlorobenzylamine **1** using manganese dioxide.

Table 1 Probing the manganese dioxide mediated benzamide formation mechanism.

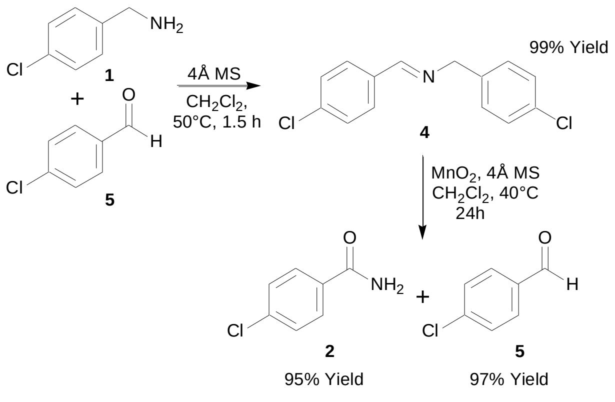
		Yield (%)[b]			
Entry	Conditions[a]	**2**	**3**	**4**	**5**
1	Standard conditions	99	≤1	≤1	≤1
2	No molecular sieves	44	16	36	3
3	Untreated MnO_2	63	≤1	37	≤1
4	12.5 equiv MnO_2	56	17	24	3
5	N_2 atmosphere	71	≤1	29	≤1
6	Recycled MnO_2	73	≤1	27	≤1
7	Aq NH_3, Untreated MnO_2	66	≤1	33	≤1
8	NH_3 in THF Untreated MnO_2	70	24	5	≤1
9	NH_3 in THF No molecular sieves	77	23	≤1	≤1

[a] Standard reaction conditions: Amine (0.5 mmol), acid washed MnO_2 (25 equiv.), 4Å molecular sieves, CH_2Cl_2 (3.5 mL), 40°C, 24 h. [b] Yields determined by ^{1}H NMR analysis.

The importance of pre-treating the manganese dioxide catalyst is seen when the reaction is repeated with commercial catalyst, the drop in amide yield to 63% being significant (Entry 3). Decreasing the catalyst loading to 12.5 equivalents also has a significant impact on amide formation (Entry 4). Surprisingly, when the reaction is conducted under an inert nitrogen atmosphere the reaction proceeds with a good, though reduced yield (71%) of amide **2** being formed (Entry 5). This result is reproducible and indicates that the oxygen for the reaction is not coming from the air but rather from oxygen already bound to the surface of the manganese dioxide catalyst.[26] The recycling of the manganese dioxide catalyst (Entry 6) results in decreased conversion to amide **2** (73% yield), though the product distribution is simpler compared to when a reduced catalyst loading is used (Entry 4). The mechanism proposed by Wang for the dehydrogenation-hydration reaction requires the addition of aqueous ammonia for conversion to the corresponding amide, which was demonstrated experimentally.[22] However, we see little improvement in yield (Entry 7) when aqueous ammonia is used in combination with untreated manganese dioxide, compared to when untreated manganese dioxide is used (Entry 3). Repeating this experiment using a 0.5M solution of ammonia in THF, where the dielectric constant of THF and the dichloromethane solvent are more closely matched, results in a modest increase in amide formation (70% yield) with a change in product distribution favouring nitrile **3** over alkylimine **4** (Entry 8). The same product distribution is observed when activated manganese dioxide is used with 0.5M ammonia in THF in the absence of molecular sieves (Entry 9).

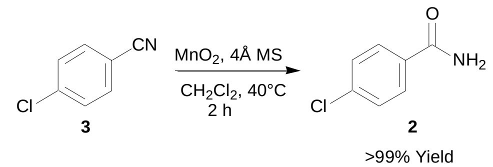
Since the reaction is essentially being carried out in an open flask we were able to sample the reaction mixture at a range of time points, utilising ^{1}H NMR spectroscopy to monitor the progress of the reaction. After one hour all intermediates proposed by Wang could be identified in the ^{1}H and ^{13}C spectra. Aldehyde **5** was only visible in trace amounts whereas the other intermediates, nitrile **3** and alkylimine **4** appeared as intense signals. After one hour, a small amount of amide **2** had been formed; this increases gradually as the signals for alkylimine **4** decrease. At subsequent time points nitrile **3** could not be observed, suggesting that the hydrolysis of the nitrile to the amide occurs rapidly.

To further probe the oxidation process, alkylimine **4** was prepared from the condensation of amine **1** and aldehyde **5**. Alkylimine **4** was then subjected to the standard manganese dioxide reaction conditions and amide **2** was formed in 95% yield after 24 hours. This indicates that under the reaction conditions alkylimine **4** can undergo hydrolysis back to the amine and aldehyde precursors, with the amine available once again to participate in the manganese dioxide oxidation. The presence of additional ammonia is not required for the conversion of the imine to the corresponding amide; however, a source of ammonia would be required to convert the aldehyde (Scheme 2).



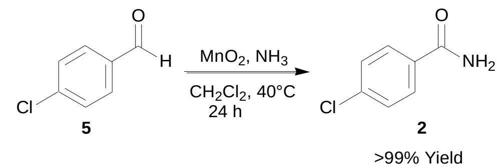
Scheme 2 Manganese dioxide mediated oxidation of imine **4**.

Subjecting nitrile **3** to the standard manganese dioxide reaction conditions employed previously results in quantitative conversion to amide **2** in 2 hours (Scheme 3). This indicates that the hydrolysis takes place without the need to provide an additional, external source of water.



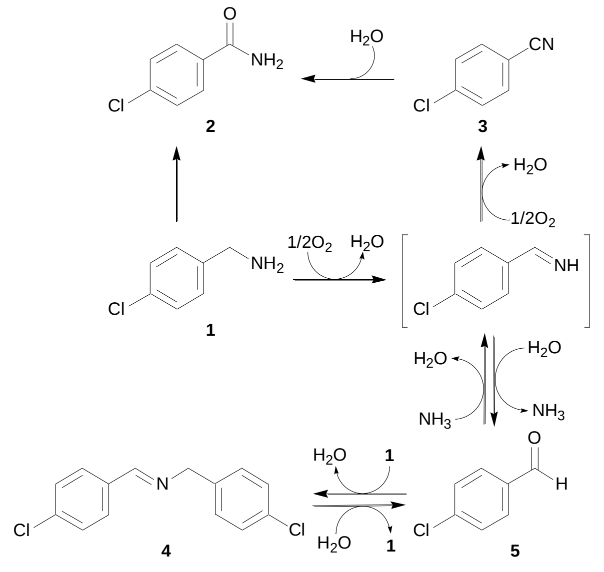
Scheme 3 Manganese dioxide mediated hydrolysis of nitrile **3**.

Treatment of aldehyde **5** with the pre-treated manganese dioxide catalyst and ammonia (0.5M in THF, 1.5 equivalents) in both the presence and the absence of molecular sieves, yields amide **2** in quantitative yield after 24 hours (Scheme 4). This demonstrates that for the oxidation of 4-chlorobenzylamine **1** to amide **2** the ammonia for the conversion of aldehyde **5** does not need to originate from the starting amine, an external source of ammonia will facilitate the conversion.



Scheme 4 Manganese dioxide mediated amidation of aldehyde **5**.

The ability to observe each of the intermediates proposed by Wang[22] (Scheme 5) as the reaction proceeds has allowed us to confirm his proposed mechanism but also to provide a greater insight into the nature of the reagents used.



Scheme 5 Mechanism proposed by Wang for the conversion of primary amines to primary amides.[22]

From the reactions conducted we believe that manganese dioxide is not only participating as a catalyst for the oxidative transformation but is also providing a source of both water and oxygen for the reaction. Even after drying, manganese dioxide is known to retain bound water[26] and it is this bound water that is intimately involved in the individual hydrolysis steps as we have shown experimentally (Scheme 2 and 3). If the molecular sieves were efficient in removing all water present then the reaction would not proceed, neither would the reaction where imine **4** is converted to amide **2** and aldehyde **5**, or the reaction where aldehyde **5** is converted to amide **2** under the same reaction conditions. Similarly, when the reaction is conducted under an inert atmosphere, if the oxygen required for the reaction were coming from the air, no product formation would be observed; the manganese dioxide is therefore acting as a dual reagent source during the reaction, supplying both oxygen and water. The importance of the manganese dioxide in this role is further demonstrated when the amount of manganese dioxide used in the reaction is reduced and the yield of amide **2** formed after 24 hours decreases. This decrease is not due to a slowing of the reaction, indeed if the reaction time is extended there is only a slight increase in product formation. Using a lower stoichiometry of manganese dioxide means that less bound water and oxygen is available for the reaction. Therefore, when this has been consumed, the reaction stops as does the interconversion of intermediates. When manganese dioxide is recycled from one reaction, reactivated and used in a repeat experiment, there is a reduction in product formation, but only a trace of nitrile **3** is observed. This implies that the problem here is not the availability of bound water but the availability of bound oxygen for the formation of nitrile **3**. The formation of imine **4** is a facile process and from the ^{1}H NMR experiments we know that the lifetime of aldehyde **5** is short. Once formed, the aldehyde is locked away as the imine this accounts for the presence of the imine when there is insufficient oxygen for complete conversion to amide **2**.

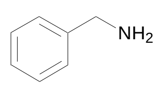
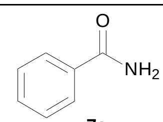
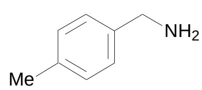
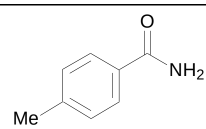
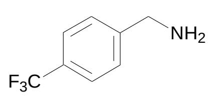
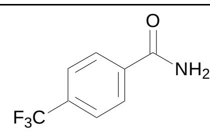
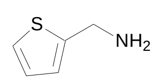
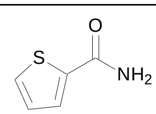
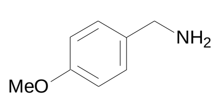
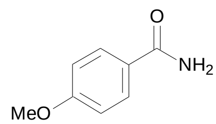
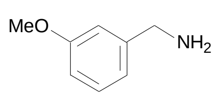
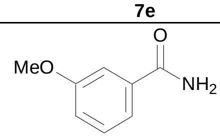
Although we see the formation of imine **4** in our ^{1}H NMR experiments it is notable that we do not need to provide additional ammonia to the reaction as is the case with the Wang approach.[22] With near quantitative conversion to the product amide the ammonia released upon formation of aldehyde **5** must be available for conversion back again. The molecular sieves are vital in this reaction and are acting as an ammonia store through the adsorption of the ammonia upon aldehyde formation. Molecular sieves are zeolites and contain acidic sites in addition to the pores which are well suited to accommodate water molecules; the molecular sieves are therefore fulfilling a dual role in the reaction. Ammonia is known to be adsorbed on the surface of zeolites as the NH_4^+ ion,[27] but with a diameter of 3.26 Å, ammonia molecules can also be accommodated within the zeolite pores.[28] When the molecular sieves are excluded from the reaction there is a significant decrease in product formation, not only is the water being produced by the reaction deactivating the manganese dioxide[8] but the ammonia is being lost from the reaction mixture as it is not being adsorbed and cannot react with aldehyde **5**. Water promotes the formation of both imine **4** and amide **2**, there is therefore a balance between these two reactions which the molecular sieves maintain. Although it is desirable to remove all water to prevent the formation of aldehyde **5**, water is essential for the hydrolysis of nitrile **3**.

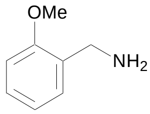
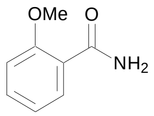
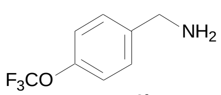
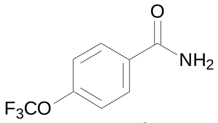
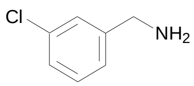
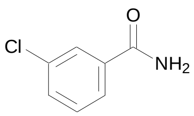
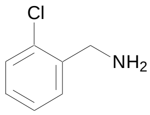
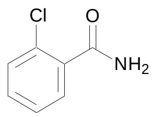
The addition of aqueous ammonia to the reaction does not increase the formation of amide **2** when "unactivated manganese dioxide" is used; in this case the reaction is biphasic with the ammonia molecules being highly solvated in the aqueous phase, making transfer to the organic phase unlikely. Furthermore, the excess water is also likely to negatively affecting both the manganese dioxide and molecular sieves.

When ammonia in THF is used in the reaction there is an excess of available ammonia which will compete with amine **1** to react with aldehyde **5**. The formation of imine **4** is reversible and as the reaction proceeds, the concentration of amine **1** will decrease due to the formation of amide **2**, hence when aldehyde **5** is formed it will be converted more readily to nitrile **3** *via* benzimine and not to imine **4**. When an external source of ammonia is utilized in the reaction, molecular sieves are not required to capture the precious ammonia as there is now sufficient ammonia present to convert aldehyde **5** to amide **2**; the reaction occurs equally well if molecular sieves are not present. It is noteworthy that even when using the pre-treated manganese dioxide, significant nitrile **3** is observed after 24 hours. Since we have demonstrated that for this substrate hydrolysis of nitrile **3** is facile, we conclude that the excess ammonia in solution is impeding the donation of water from the manganese dioxide.

The application of our method to a diverse range of substrates has been investigated (Table 2). For benzylamine **6g**, in addition to the anticipated amide **7g**, the intermediate nitrile **8g** is also isolated (28% yield) after 24 hours. We believe that the hydrolysis of this intermediate is slower due to steric crowding of the benzylic carbon by the methoxy-group which results in a reduced yield of amide **7g** after 24 hours.

Table 2 Manganese dioxide mediated benzamide formation.

Entry	Substrate	Product[a,b]	Yield (%)[c]
1	 **6a**	 **7a**	98
2	 **6b**	 **7b**	98
3	 **6c**	 **7c**	87
4	 **6d**	 **7d**	98
5	 **6e**	 **7e**	93
6	 **6f**	 **7f**	83

7	 6g	 7g	69
8	 6h	 7h	88
9	 6i	 7i	92
10	 6j	 7j	83

[a] Standard reaction conditions: Amine (1 mmol), acid washed MnO_2 (25 mmol), 4Å MS, CH_2Cl_2 (7 mL), 40°C, 24 h. [b] All products were characterized by NMR (^{1}H and ^{13}C), IR, and melting point. [c] Isolated yield.

The scale of the reaction can be increased without significantly affecting the yield of amide formed. The reaction of 19 mmol benzylamine **6a** gave amide **7a** in a 96% yield; compared with 98% at a 1 mmol scale, further demonstrating the synthetic utility of this procedure.

Conclusions

In summary, we have prepared a series of substituted benzamides *via* an oxidative dehydrogenation-hydration strategy from the corresponding benzylamine mediated by manganese dioxide. The reaction conditions for the transformation are mild and do not require high reaction temperatures or high pressure reaction vessels. The reaction utilises reagents that are commercially available and which can be prepared using standard laboratory apparatus. The mild reaction conditions have allowed us to probe the mechanism for this transformation for the first time, and have given a deeper insight into the role of both manganese dioxide and molecular sieves in oxidation reactions.

Experimental Section

General Experimental Details

Infrared spectra were obtained on a Perkin Elmer 100 FTIR Spectrometer operating in ATR mode. Only significant absorptions (ν_{max}) are reported and all absorptions are recorded in wavenumbers (cm^{-1}). Melting points were measured with an Electrothermal apparatus and are uncorrected.

Proton magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz using a Bruker spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm) and are referenced to the residual protonated solvent peak. The order of citation in parentheses is (i) number of equivalent nuclei (by integration), (ii) multiplicity (s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet), (iii) coupling constant (J) quoted in Hertz (Hz) to one decimal place, (iv) assignment. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100.6 MHz using a Bruker spectrometer. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the appropriate solvent peak. The assignment is quoted in parentheses.

Flash Chromatography was carried out using silica gel (Aldrich, 230-400 mesh) as the stationary phase. Thin Layer Chromatography was carried out on aluminium plates pre-coated with silica (Merck silica gel 60 F_{254} on aluminium) which was visualized by the quenching of ultraviolet fluorescence (λ_{max}=254 nm) and/or by staining with potassium permanganate solution followed by heat.

All reactions were carried out at atmospheric pressure with stirring unless otherwise stated. Molecular sieves were purchased from *Alfa Aesar* (Cat.No. L05512.30, Molecular sieves, 4Å, 0.4-0.8 mm (0.02-0.03 in) beads, 250 g). All reagents were used as received unless otherwise stated. The fractions of light petroleum ether boiling between 40 and 60°C are referred to as 'hexanes'.

Preparation of activated manganese dioxide

Manganese dioxide was purchased from *Alfa Aesar* (Cat. No. 014340.22, Manganese(IV) oxide, activated, tech., Mn 58% min, 100 g) and further activated by treatment with dilute nitric acid: MnO_2 (50 g) was placed on a large Büchner funnel and 10% nitric acid (80 mL) was added slowly. After the addition was completed, the MnO_2 cake was washed with a large amount of water (2-3 L) or until the filtrate was neutral. The MnO_2 was subsequently dried at 105°C for two days and could be stored under normal laboratory conditions for several weeks without loss of activity.

4-Chlorobenzamide 2

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-chlorobenzylamine **1** (142 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). Concentration under reduced pressure gave 4-chlorobenzamide 2 (152 mg, 98%) as a white solid.

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added *N*-(4-chlorobenzylidene)-1-(4-chlorophenyl)methanamine **4** (263 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filltered through a pad of Celite and washed with hot (60°C) methanol (250 mL). Concentration under reduced pressure and recrystallisation (hexane) gave 4-chlorobenzamide **2** (148 mg, 95%) as a white solid. Concentration of the hexane filltrate under reduced pressure gave 4-chlorobenzaldehyde **5** (136 mg, 97%) as a white solid.

4-Chlorobenzamide **2**: mp 176-177°C; ν_{max} (solid) 3368 (N-H), 3177 (N-H), 1658 (C=O), 1620, 1568, 1493, 1407, 1388, 1089, 1013 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.06 (1H, s, -CONH), 7.89 (2H, d, J 8.3 Hz, *ortho* Ar-H), 7.53 (2H, d, J 9.6 Hz, *meta* Ar-H), 7.47 (1H, s, -CONH); δ_C (100.6 MHz, DMSO-d_6) 166.78 (C=O), 136.04 (*para* Ar), 133.00 (*ipso* Ar), 129.38 (*meta* Ar), 128.28 (*ortho* Ar). *In agreement with published data*.[24,25]

4-Chlorobenzaldhyde **5**: mp 43-46°C; ν_{max} (solid) 1690 (C=O), 1575, 1386, 1292, 1206, 1153, 1092, 1011, 838, 813 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 10.00 (1H, s, CHO), 7.94-7.91 (2H, m, *ortho* Ar-H), 7.68-7.65 (2H, m, *meta* Ar-H); δ_C (100.6 MHz, DMSO-d_6) 192.15 (CHO), 139.40 (*para* Ar), 134.85 (*ipso* Ar), 131.20 (*ortho* Ar), 129.38 (*meta* Ar). *In agreement with published data.*[29]

N-(4-Chlorobenzylidene)-1-(4-chlorophenyl)methanamine 4

To a suspension of 4Å molecular sieves (3.00 g) in dichloromethane (30 mL) was added 4-chlorobenzaldehyde (1.66 g, 11.8 mmol, 1.0 equiv) and 4-chlorobenzylamine (1.67 g, 11.8 mmol, 1.0 equiv). The reaction was stirred at 40°C for 1.5 h. The molecular sieves were filtered off and washed with acetone (8 mL). Concentration under reduced pressure gave *N*-(4-chlorobenzylidene)-1-(4-chlorophenyl) methanamine **4** (3.05 g, 99%) as a white solid; mp 62-64°C; ν_{max} (solid) 2817, 1642, 1593, 1568, 1489, 1428, 1404, 1372, 1090, 1047, 1013, 862 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.50 (1H, s, Ar-CH=N-), 7.79 (2 H, d, J 8.6 Hz, 1 x Ar-H), 7.52 (2 H, d, J 8.4 Hz, 2 x Ar-H), 7.41-7.34 (4 H, m, 2 x Ar-H), 4.76 (2H, s, N-CH_2-Ar); δ_C (100.6 MHz, DMSO-d_6) 161.11, 138.55, 135.48, 134.80, 131.45, 129.72, 129.68, 128.86, 128.36, 62.90. *In agreement with published data*.[30]

Benzamide 7a

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added benzylamine (107 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). Concentration under reduced pressure and recrystallisation (hexane) gave benzamide **7a** (119 mg, 98%) as a white solid.

To a suspension of 4Å molecular sieves (10.0 g) in dichloromethane (130 mL) was added benzylamine (2.00 g, 18. 7 mmol, 1.0 equiv). Manganese dioxide (40.57 g, 466.6 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (600 mL). Concentration under reduced pressure and recrystalisation (hexane) gave benzamide **7a** (2.18 g, 96%) as a white solid.

Benzamide **7a**: mp 125-127°C; ν_{max} (solid) 3360 (N-H), 3162 (N-H), 3062, 1651 (C=O), 1618, 1575, 1448, 1296, 1178, 1141, 1120, 1024, 917 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.99 (1H, s, -CONH), 7.88 (2H, d, J 8.4 Hz, *ortho* Ph-H), 7.52 (1H, t, J 7.3 Hz, *para* Ph-H), 7.45 (2 H, t, J 7.4 Hz, *meta* Ph-H), 7.37 (1 H, s, -CONH); δ_C (100.6 MHz, DMSO-d_6) 167.91 (C=O), 134.26 (*ipso* Ph), 131.24 (*para* Ph), 128.23 (*meta* Ph), 127.47 (*ortho* Ph). *In agreement with published data.*[31,32]

4-Methylbenzamide 7b

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-methylbenzylamine (121 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). Concentration under reduced pressure afforded 4-methylbenzamide **7b** (132 mg, 98%) as a white solid; mp 159-160°C; ν_{max} (solid) 3337 (N-H), 3157 (N-H), 2929, 1666 (C=O), 1613, 1568, 1411, 1395, 1189, 1144, 1123, 1021 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.89 (1H, s, -CONH), 7.77 (2 H, d, J 8.1 Hz, *ortho* Ar-H), 7.24 (3H, d, J 8.0 Hz, *meta* Ar-H and -CONH), 2.34 (3H, s, CH_3); δ_C (100.6 MHz, DMSO-d_6) 167.78 (C=O), 141.07 (*para* Ar), 131.47 (*ipso* Ar), 128.74 (*meta* Ar), 127.51 (*ortho* Ar), 20.96 (-CH_3). *In agreement with published data.*[32,33]

4-Trifluoromethylbenzamide 7c and *p*-trifluoromethyl-*N*-[*p*-(trifluoromethyl)-benzylidene]-benzylamine 8c

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-trifluoromethylbenzylamine (175 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). The filtrate was concentrated under reduced pressure and the crude product washed with a hexane (5 mL). 4-Trifluoromethylbenzamide **7c** was obtained as a white solid (165 mg, 87%). Concentration of the hexane filtrate under reduced pressure gave *p*-trifluoromethyl-*N*-[*p*-(trifluoromethyl)-benzylidene]-benzylamine **8c** (21 mg, 12%) as a pale yellow solid.

4-Trifluoromethylbenzamide **7c**: mp 182-184°C; ν_{max} (solid) 3375 (N-H), 3177 (N-H), 1655 (C=O), 1627, 1579, 1516, 1418, 1322, 1067, 1016 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.21 (1H, s, -CONH), 8.06 (2H, d, J 8.1 Hz, *ortho* Ar-H), 7.83 (2H, d, J 8.2 Hz, *meta* Ar-H), 7.63 (1H, s, -CONH); δ_C (100.6 MHz, DMSO-d_6) 166.73 (C=O), 138.11 (*ipso* Ar), 131.18 (q, *para* Ar, $^2J_{CF}$ 32 Hz), 128.37 (*ortho* Ar), 125.31 (q, *meta* Ar, $^3J_{CF}$ 3.2 Hz), 122.65 (one peak from q, -CF_3); δ_F (376 MHz, DMSO-d_6) -61.30. *In agreement with published data*.[32,34]

p-Trifluoromethyl-*N*-[*p*-(trifluoromethyl)-benzylidene]-benzylamine **8c**: mp 35-36°C; ν_{max} (film) 2929, 2855, 1650 (imine), 1620, 1583, 1418, 1377, 1326, 1222, 1166, 1126, 1067, 1019, 953, 839 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.47 (1H, s, Ar-CH=N-), 7.91 (2H, d, J 8.1 Hz, Ar-H), 7.69 (2 H, d, J 8.2 Hz, Ar-H), 7.62 (2H, d, J 8.1 Hz, Ar-H), 7.47 (2 H, d, J 8.0 Hz, Ar-H), 4.90 (2H, s, N-C<u>H</u>$_2$-Ar); δ_C (100.6 MHz, $CDCl_3$) 161.26 (Ar-<u>C</u>H=N-), 143.11 (*ipso* Ar-CH=N-), 139.10 (*ipso* Ar-CH_2N), 132.71 (q, *para* Ar-CH=N-, $^2J_{CF}$ 32.4 Hz), 129.57 (q, *para* Ar-CH_2N, $^2J_{CF}$ 32.4 Hz), 128.66 (*ortho* Ar-CH=N-), 128.26 (*ortho* Ar-CH_2N), 125.80 (q, *meta* Ar-CH=N-, $^3J_{CF}$ 3.8 Hz), 125.63 (q, *meta* Ar-CH_2N, $^3J_{CF}$ 3.8 Hz), 124.02 (q, -CF_3, $^1J_{CF}$ 272.3 Hz), 64.55 (N-<u>C</u>H$_2$-Ar). *In agreement with published data*.[35,36]

Thiophene-2-carboxamide 7d

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 2-(aminomethyl)-thiophene (113 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). Concentration under reduced pressure afforded thiophene-2-carboxamide **7d** (125 mg, 98%) as a white solid; mp 176-178°C; ν_{max} (solid) 3356 (N-H), 3164 (N-H), 1650 (C=O), 1601, 1524, 1429, 1392, 1242, 1123, 1096, 1041, 858 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.98 (1H, s, -CON<u>H</u>), 7.75-7.73 (2H, m, H-3 and H-5), 7.38 (1H, s, -CON<u>H</u>), 7.12 (1H, t, J 4.1 Hz, H-4); δ_C (100.6 MHz, DMSO-d_6) 162.90 (C=O), 140.35 (C2), 131.01 (C3), 128.70 (C5), 127.93 (C4). *In agreement with published data.*[37,38]

4-Methoxybenzamide 7e

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-methoxybenzylamine (137 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). The solvent was removed under reduced pressure and the crude product purified by column chromatography (ethyl acetate:hexane, 1:1 → 4:1). 4-Methoxybenzamide **7e** (140 mg, 93%) was obtained as a white solid; mp 165-167°C; ν_{max} (solid) 3387 (N-H), 3159 (N-H), 2843, 1641 (C=O), 1615, 1572, 1515, 1457, 1421, 1391, 1308, 1249, 1190, 1179, 1145, 1114, 1023, 848 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.84 (3H, d, J 8.7 Hz, *ortho* Ar-H and -CON<u>H</u>), 7.18 (1H, s, -CON<u>H</u>), 6.97 (2H, d, J 8.7 Hz, *meta* Ar-H), 3.79 (3H, s, -OCH_3); δ_C (100.6 MHz, DMSO-d_6) 167.47 (C=O), 161.61 (*para* Ar), 129.39 (*ortho* Ar), 126.51 (*ipso* Ar), 113.41 (*meta* Ar), 55.35 (-OCH_3). *In agreement with published data*.[32]

3-Methoxybenzamide 7f

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 3-methoxybenzylamine (137 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). The solvent was removed under reduced pressure and the crude was purified by column chromatography (ethyl acetate:hexane, 1:1 → 4:1). 3-Methoxybenzamide **7f** (125 mg, 83%) was obtained as a white solid; mp 131-133°C; ν_{max} (solid) 3128, 1664 (C=O), 1627, 1581, 1463, 1429, 1330, 1247, 1131, 1030, 902, 877 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.96 (1H, s, -CON<u>H</u>), 7.33- 7.46 (4H, m, 3 x Ar-H and -CON<u>H</u>), 7.08 (1H, ddd, J 8.1 Hz, 2.6 Hz, 0.8 Hz, H-6), 3.79 (3H, s, -OCH_3); δ_C (100.6 MHz, DMSO-d_6) 167.64 (C=O), 159.14 (C1), 135.73 (C3), 129.33 (C5), 119.69 (C4), 117.07 (C6), 112.63 (C2), 55.23 (-OCH_3). *In agreement with published data.*[34]

2-Methoxybenzamide 7g and 2-methoxybenzonitrile 8g

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 2-methoxybenzylamine (137 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). The solvent was removed under reduced pressure and the crude product purified by column chromatography (ethyl acetate:hexane, 1:1 → 3:1). 2-Methoxybenzamide **7g** (104 mg, 69%) was obtained as a white solid and 2-methoxybenzonitrile **8g** (37 mg, 28%) was obtained as a colourless oil.

2-Methoxybenzamide **7g**: mp 126-128°C; ν_{max} (solid) 3410 (N-H), 3190 (N-H), 3013, 2980, 2948, 2840, 1623 (C=O), 1597, 1573, 1488, 1462, 1434, 1394, 1274, 1240, 1179, 1106, 1020 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.79 (1H, dd, J 7.7 Hz, 1.8 Hz, H-3), 7.63 (1H, s, -CON<u>H</u>), 7.52 (1H, s, -CON<u>H</u>), 7.45-7.49 (1H, m, H-5), 7.12 (1H, d, J 10.0 Hz, H-6), 7.02 (1H, td, J 7.6 Hz, 0.9 Hz, H-4), 3.88 (3H, s, -OCH_3); δ_C (100.6 MHz, DMSO-d_6) 166.34 (C=O), 157.24 (C1), 132.48 (C5), 130.74 (C3), 122.73 (C4), 120.41 (C2), 111.99 (C6), 55.82 (-OCH_3). *In agreement with published data.*[32,39]

2-Methoxybenzonitrile **8g**: ν_{max} (film) 2975, 2948, 2843, 2228 (CN), 1688, 1599, 1494, 1465, 1290, 1262, 1021, 758 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25-7.72 (2H, m, H-3 and H-5), 6.64-7.16 (2H, m, H-4 and H-6), 3.87 (3H, m, -OCH_3); δ_C (100.6 MHz, $CDCl_3$) 161.25 (C1), 134.39 (C5), 133.79 (C3), 120.77 (C4), 116.52 (C6), 111.27 (CN), 101.83 (C2), 56.00 (-O<u>C</u>H$_3$). *In agreement with published data*.[40,41]

4-Trifluoromethoxybenzamide 7h

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 4-trifluoromethoxybenzylamine (191 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). The solvent was removed under reduced pressure and the crude product purified by column chromatography (ethyl acetate:hexane, 1:1 → 3:1). 4-Trifluoromethoxybenzamide **7h** (181 mg, 88%) was obtained as a white solid; mp 152-154°C; ν_{max} (solid) 3372 (N-H), 3172 (N-H), 1652 (C=O), 1622, 1585, 1510, 1419, 1397, 1207, 1153, 1015, 926, 858 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.11 (1H, s, -CON<u>H</u>), 8.00 (2H, d, J 8.7 Hz, *ortho* Ar-H), 7.51 (1H, s, -CON<u>H</u>), 7.45 (2H, d, J 8.3 Hz, *meta* Ar-H); δ_C (100.6 MHz, DMSO-d_6) 166.59 (C=O), 150.26 (*para* Ar), 133.37 (*ipso* Ar), 129.75 (*ortho* Ar), 120.50 (*meta* Ar), 119.93 (q, -OCF_3, $^1J_{CF}$ 255 Hz); δ_F (376 MHz, DMSO-d_6) -56.68. *In agreement with published data*.[42]

3-Chlorobenzamide 7i

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 3-chlorobenzylamine (142 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). Concentration under reduced pressure and recrystallisation (hexane) gave 3-chlorobenzamide **7i** (142 mg, 92%) as a white solid; mp 132-134°C; ν_{max} (solid) 3347 (N-H), 3167 (N-H), 1656 (C=O), 1620, 1561, 1426, 1387, 1122, 901 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.11 (1H, s, -CONH), 7.91 (1H, s, H-2), 7.83 (1H, d, J 7.7 Hz, H-4), 7.59 (1H, d, J 8.0 Hz, H-6), 7.54 (1H, s, -CONH), 7.49 (1H, t, J 7.9 Hz, H-5); δ_C (100.6 MHz, DMSO-d_6) 166.44 (C=O), 136.32 (C3), 133.16 (C1), 131.12 (C6), 130.30 (C5), 127.33 (C2), 126.22 (C4). *In agreement with published data*.[25]

2-Chlorobenzamide 7j

To a suspension of 4Å molecular sieves (800 mg) in dichloromethane (7 mL) was added 2-chlorobenzylamine (142 mg, 1.00 mmol, 1.0 equiv). Manganese dioxide (2.17 g, 25.0 mmol, 25.0 equiv) was added portionwise and the mixture stirred at 40°C for 24 h. The reaction mixture was filtered through a pad of Celite and washed with hot (60°C) methanol (250 mL). The solvent was removed under reduced pressure and the crude product purified by column chromatography (ethyl acetate:hexane, 1:1 → 4:1). 2-Chlorobenzamide **7j** (128 mg, 83%) was obtained as a white solid; mp 139-141°C; ν_{max} (solid) 3357 (N-H), 3172 (N-H), 1638 (C=O), 1563, 1480, 1432, 1401, 1119, 1047, 953 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.87 (1H, s, -CONH), 7.59 (1H, s, -CONH), 7.35-7.47 (4H, m, 4 x Ar-H); δ_C (100.6 MHz, DMSO-d_6) 168.17 (C=O), 137.17 (C2), 130.56 (C5), 129.62 (C1), 129.60 (C6), 128.66 (C3), 127.03 (C4). *In agreement with published data.*[33]

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Notes and References

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