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Bifunctional solid catalysts for chemoselective hydrogenation–cyclisation–amination cascade reactions of relevance for the synthesis of pharmaceuticals

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ABSTRACT

The benzodiazepines olanzapine and clozapine are nowadays manufactured by a three-step process with a final yield below 50%. An approach to environmentally-friendly intensive processes consists in the development of multifunctional solid catalyst able to catalyze multistep reactions. Here, a bifunctional metal-acid solid catalyst has been prepared and is able to carry out hydrogenation–cyclisation–amination reactions in a cascade process. The catalytic system is illustrated for the synthesis of these important antipsychotics, being an alternative for the current industrial process that requires three steps batch reactions, using mineral acids and bases, and stoichiometric amounts of $SnCl_2$.

1. Introduction

The use of recoverable solid catalysts is not common for the synthesis of complex molecules.[1] To our knowledge, there are only a limited number of examples of complex molecules that present more than two solid-catalysed consecutive steps during their synthesis,[2,3] in particular bifunctional catalysts. Most often, the synthesis of potential drugs is performed with homogeneous catalysts, which are known to catalyse chemo-, regio- and stereoselective reactions.[4]

In the last years, the design and development of structured solid materials with well-defined catalytic sites has experienced important advances[5] and highly active and, more importantly, highly selective solid catalysts have been prepared.[6,7] However, in most cases, application of these catalysts is limited to relatively simple reactions with standard substrates, and preparation of more complex molecules, including drugs, remains scarce.

Schizophrenia is an important mental disorder in developed countries, imparting severe personal and social dysfunction to people. It is calculated that 1% of the population can suffer the illness. Two of the most used drugs for its treatment are the benzodiazepines olanzapine **1** and clozapine **2** (Fig. 1), which are known as atypical antipsychotics.[8] Compound **1** is a top-ten best-seller drug marketed by Eli Lilly & Co.[9] for the treatment of schizophrenia and bipolar disorder and **2** is indicated for treatment-resistant schizophrenia when other drugs have failed.[10]

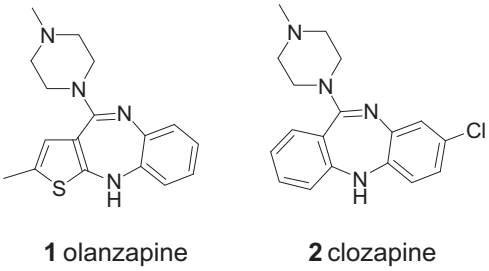

Figure 1. Structure of the benzodiazepines whose syntheses are studied in this work.

Syntheses of **1** and **2** are based on three batch processes that involve the use of mineral acids and bases, as well as other polluting chemicals such as $SnCl_2$ in stoichiometric amounts. Therefore, it would be of interest to substitute all these reagents by a solid catalyst that could perform the three reactions, i. e., chemoselective hydrogenation, cyclisation and amination, in one-pot through a cascade process. Such a process should require a bifunctional catalyst with metal and acid sites. Therefore, we have prepared a high surface area structured aluminosilicate, supporting metal

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nanoparticles, that is, able to couple the three steps in just one, while: (1) avoiding the use of pollutant stoichiometric reagents, (2) decreasing by-products and avoiding solvents and (3) saving energy. The different solids tested as catalysts in this work are listed in Table 1.

Table 1
List of acid solids employed in this work as catalysts with some of their physicochemical properties

Solid	Si/Al	BET surface ($m^2 \times g^{-1}$)
SiO_2–Al_2O_3	6	<100
Al–MCM-41	15	680
	60	1100
ITQ-2	15	620
	25	710
	50	850
TiO_2	—	<100
ZrO_2–SO_4	—	100

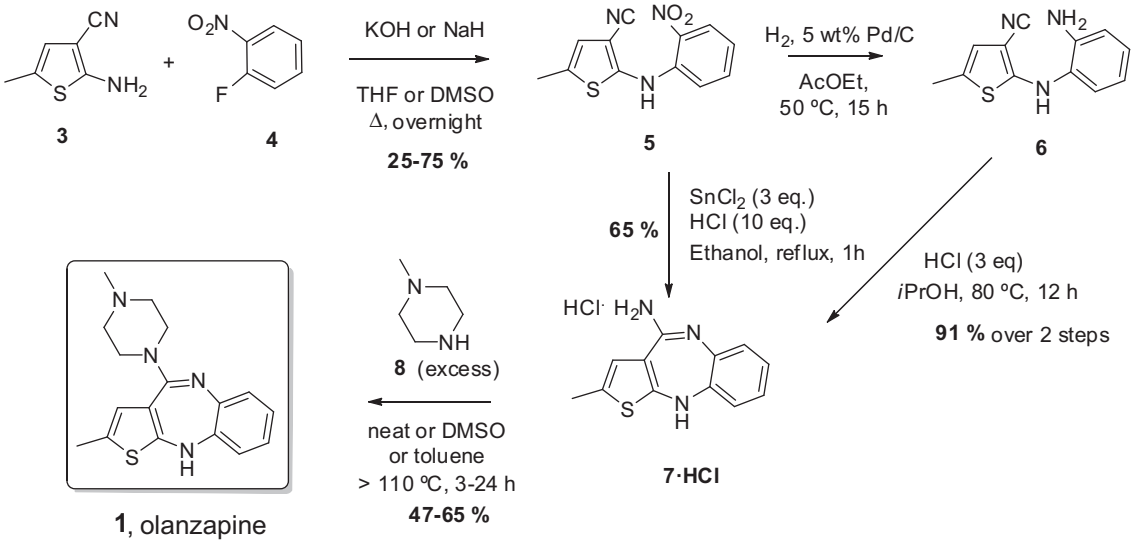
2. Results and discussion

2.1. Olanzapine

The general synthetic routes for olanzapine **1**, including the industrial one, are given in Scheme 1.[9,11]

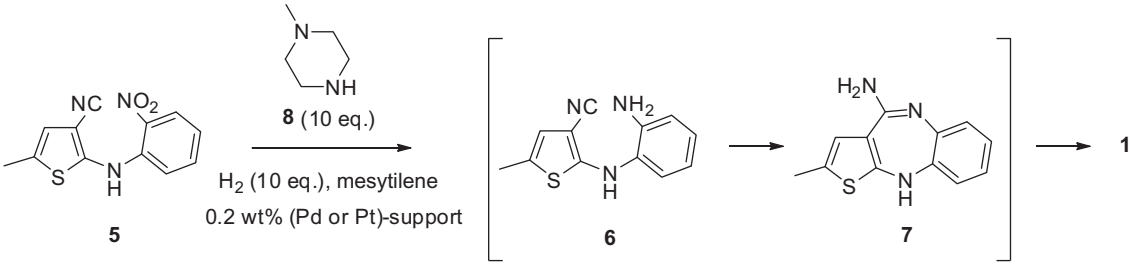
cyclisation with HCl in excess.[13] However, a catalytic hydrogenation of the nitro group with Pd/C followed by cyclisation in alcoholic HCl solution to produce **7**·**HCl** was claimed in a later patent. Finally, olanzapine **1** is obtained from **7**·**HCl** at high temperatures and long reaction times. The overall yield of olanzapine **1** from the common intermediate **5** in the industrial synthesis was below 48%, while 2 Kg of by-products per Kg of olanzapine **1** were produced. We have envisaged the use of a bifunctional solid catalyst with enough acidity for the Brönsted-catalysed steps and metal nanoparticles (Pt or Pd) for the hydrogenation step (Scheme 2). This solid could provide all the catalytic active sites needed to get **1** directly from **5**. Starting with this idea, a series of solid acids with sites of different strength were prepared and their characteristics are given in Table 1. Pt and Pd were then incorporated to the acid supports (see Experimental)[7,14] and the first set of results are given in Table 2.

It can be seen there that olanzapine **1** could be obtained from **5** in one-pot though still with lower yields than those reported in the patent literature for the three-step process. Importantly, we have observed that amine **8** can be present in the reaction mixture from the beginning, rendering the set-up easier. The cascade reaction with the bifunctional solid catalyst starts with the chemoselective hydrogenation of the nitro group in **5** to form the amine **6**, which cyclises to the imine **7** under acid conditions. Finally, a second acid-



Scheme 1. Reported syntheses of olanzapine **1**.

The key compound for the formation of the thienobenzodiazepine ring is the diarylamine **5**, which is obtained by nucleophilic substitution of amine **3** on fluoride **4**.[12] In the original patent, **5** is directly transformed to aminobenzodiazepine **7**·**HCl** by reduction of the nitro group with stoichiometric amounts of $SnCl_2$ and later catalyzed process, namely transamination of **8** with the amine group in **7**, gives **1**. The Pt-supported on sulfated acid zirconia and amorphous or structured Al–MCM-41 silica–alumina,[15] which present different acidities[15c,16] (entries 1–3) were able to form the thienobenzodiazepine ring **7** at 140 °C under H_2. Unfortunately,



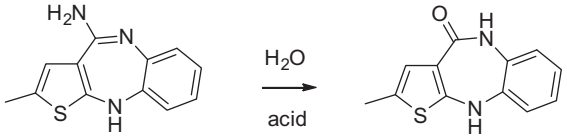
Scheme 2. Proposed one-pot synthesis of olanzapine **1**.

Table 2
One-pot synthesis of olanzapine **1** using bifunctional solid catalysts

Entry	Metal/Support	T (°C)	Reaction Time (h)	H_2 (h)	**1** (%)	**6** (%)	**9** (%)	Others (%)
1	Pt^{IV}/ZrO_2-SO_4	140	24	24	—	6	83	11
2	$Pt^{IV}/SiO_2-Al_2O_3$[a]				3	2	48	44
3	Pt^{IV}/Al–MCM-41[b]				5	13	54	28
4	Pt^{IV}/ITQ-2[c]				9	48	10	30
5	Pt^{IV}/TiO_2				—	—	—	—
6	Pt^{0}/TiO_2				1	50	10	39
7	Pd^{0}/TiO_2				8	—	14	78
8	Pt^{IV}/ITQ-2[c]	140	48	16	6	12	58	24
9	Pt^{IV}/ITQ-2[d]			16	6	13	56	29
10	**Pt^{IV}/ITQ-2**[c,e]	**160**		**24**	**35 (20)**[f]	**<5**	**25**	**35**
11	Pt^{IV}/ITQ-2[c,g]			24	17	<5	55	26
12	Pt^{IV}/ITQ-2[c,h]			0.5	22	<5	40	36
13	Pt^{IV}/ITQ-2[c]		24	24	20	18	—	58
14	**Pd^{0}/TiO_2**[e,i]				**33 (25)**[f]	—	**25**	**40**
15	Pd^{0}/TiO_2[e]		48	1	25	—	20	55
16	Pd^{II}/ITQ-2[d,e]		24	24	22	27	28	49
17	Reused				7	27	—	67
18	Activated[j]				8	23	—	69

Reaction conditions: **5** (25.9 mg, 0.1 mmol), catalyst (52 mg, 1 mol % metal), *N*-methylpiperazine (110 μL, 1 mmol), mesitylene (0.5 mL), H_2 (8–10 bar) in a 2 mL conic double-walled reactor; GC yield unless otherwise indicated.
[a] Si/Al ratio ~6.
[b] Si/Al ratio ~15.
[c] Si/Al ratio ~25.
[d] Si/Al ratio ~50.
[e] Double amount of catalytic solid and solvent.
[f] Isolated yield
[g] 0.4 wt % in Pt, double amount of solvent.
[h] 0.4 wt % in Pt, triple amount of catalyst and double amount of solvent.
[i] Active in a second use.
[j] Activated at 300 °C for 1 h.

a major by-product was found. After isolation and characterization, this product was identified as the amide **9**,[11b] coming from the amidine hydrolysis in **7** (Scheme 3).



7 9

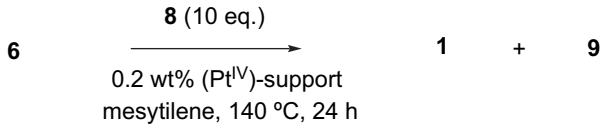
Scheme 3. Formation of the amide **9** from **7**.

However, Pt-supported over a delaminated high-surface layered aluminosilicate, such as ITQ-2,[17] having a higher surface area and stronger acidity, avoided the formation of **9** (entry 4). Similarly, Pt^{0}/TiO_2 and Pd^{0}/TiO_2 did not hydrolyze **7**, Pd being more active than Pt for the formation of **1** (entries 6 and 7). Pre-reduction of the metal at 200 °C under H_2 was needed (entry 5).[6,7,18] Regarding Pt^{IV}/ITQ-2, the yield of **1** was slightly improved by prolonging the reaction time to 48 h (entries 8 and 9). When both the amount of catalyst and the temperature were increased (entry 10), a 20% isolated yield of **1**, after preparative TLC, could be obtained. At this point, an increase in the amount of catalyst did not improve further the yield of **1** (entries 11–13).

The formation of **9** was also suppressed by using Pd^{0}/TiO_2 as catalyst, and with the mild acidity of the Ti–OH groups in TiO_2, a 25% isolated yield of **1** was obtained at 160 °C, after 24 h under H_2 (entry 14). Furthermore, the Pd^{0}/TiO_2 was recovered and reused. An increase of the reaction time did not improve the yield (entry 15). Pd^{II}/ITQ-2 was also tested as catalyst (entry 16), but the result was not better (compare entries 10 and 16), and an important loss of activity occurs during recycling (entries 17 and 18). Other hydrogenating metals such as gold (Au^{0}/TiO_2) were tested and no product was found.

With these preliminary results in hand, we can conclude that, while the competition of amine **8** and H_2O for substituting the amine group in **7** is responsible for a decrease of the final yield in the reaction sequence **7**→**1**, the one-pot synthesis of **1** from **5** is feasible. Therefore, since this step is critical in the overall process we decided to study the reactions **6**→**7**→**1** independently. Results in Table 3 show that, under our reaction conditions, the intermediate **7** could not be isolated or even detected, indicating that the substitution of the amine group is very fast, regardless of the nucleophile. Intermediate **6** was isolated by using Pt^{0}/TiO_2 as catalyst under H_2 and the crystal structure of this intermediate is shown in Figure 2 (see also Supplementary Data).

Table 3
Formation of olanzapine **1** from **6** using solid acid catalysts



Entry	Acid support[a]	Si/Al molar ratio	**1** (%)[b]	**9** (%)[b]	Other by-products (%)[b]
1	$Pt^{IV}/SiO_2-Al_2O_3$	6	5	7	—
2	Pt^{IV}/ITQ-2	15	7	9	—
3	Pt^{IV}/ITQ-2	50	18	—	5
4	ITQ-2	50	12	—	5
5	Al–MCM-41	15	21	18	—
6	Al–MCM-41	60	13	—	87[c,d]
7	H-Beta	12	—	—	50
8	H-USY	15	—	—	8
9	TiO_2	—	—	—	>99
10	Pt^{0}/TiO_2	—	24	—	54
11	Pt^{0}/TiO_2(NaCl)	—	17	—	65
12	CH_3SO_3H[e]	—	13	—	46

[a] 104 mg of solid for 0.1 mmol of **7**.
[b] GC yield, rest is unreacted starting material.
[c] Catalyst activated at 300 °C for 3 h under vacuum.
[d] Heavier products were observed.
[e] 20 mol %.

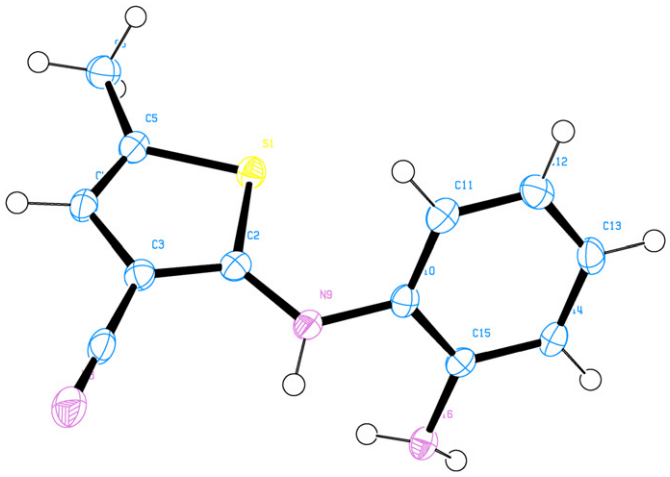
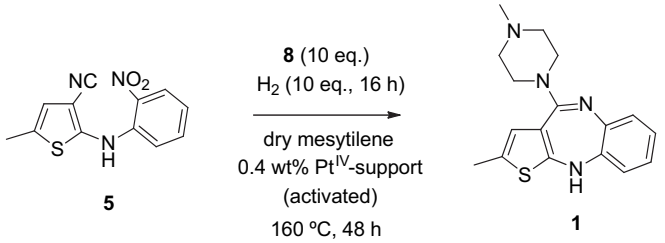


Figure 2. ORTEP visualization of amine **6**.

The nature of the acid component of the catalyst has a strong influence on the competition of amine **8** and H_2O for substituting the amino group in **7**. Indeed, amorphous silica–alumina with a very low amount of tetrahedrally coordinated alumina (and therefore bridging hydroxyl groups) and a large percentage of Al^{VI} gives low selectivity to **1** (entry 1). The two other aluminosilicates (see ^{27}Al-MAS NMR spectra in Figs. S1 and S2 in suppo. info.) with high pore accessibility, i. e. MCM-41 and ITQ-2, give better selectivity, especially when samples with higher Si/Al ratio are obtained (entries 2–6). It has to be taken into account that less catalytic sites are functional in ITQ-2 since only ~40% of the acid sites are external, the other 60% remaining inaccessible for **6**.[17a] Indeed, Al–MCM-41 showed a better activity and slightly better selectivity **1**/**9** than Pt^{IV}/ITQ-2 (compare entries 5 and 2 and entries 6 and 3 in Table 3) for a similar Si/Al ratio, although unidentified heavier by-products were found in the former (entry 6).[11b,c] Micropore zeolites, though with a high concentration of bridging hydroxyl groups, show no activity (entries 7 and 8), owing to strong diffusional limitations of reactants and product within the micropores. In fact, the dimensions of **6** (6×7×9 Å) are nearly similar to the pore opening of large pore zeolites. It has to be noticed that TiO_2 is not selective at all, while Pt^0/TiO_2 gave a good yield of **1** (entries 9 and 10). It appears that in this catalyst the Ti–OH are not responsible for the reaction but the residual acidity of the Pt atoms, since the TiO_2 completely cracks **6** into unidentified by-products. This is in accordance with the pyrolytic action of TiO_2 and related metal oxides over organic molecules at elevated temperatures. Poisoning TiO_2 with 100 ppm of NaCl did not improve the results (entry 11). It has to be mentioned that high amounts of a strong Brønsted acid such as CH_3SO_3H have to be used in order to get similar yields of **1** than with the solid acids (entry 12), and **9** was not produced under the action of this strong acid, corroborating the need of strong acid sites to improve the **1** to **9** ratio. This conclusion would be in agreement with the fact that 1 equiv of HCl is used in the industrial process to perform this reaction.[9,11a]

Taking into account the above results, the one-pot synthesis of olanzapine **1** was performed with Pt^{IV}–aluminosilicates as catalysts under anhydrous conditions (Table 4).

Table 4
Optimized one-pot synthesis of olanzapine **1** using Pt^{IV}-aluminosolicates as catalysts



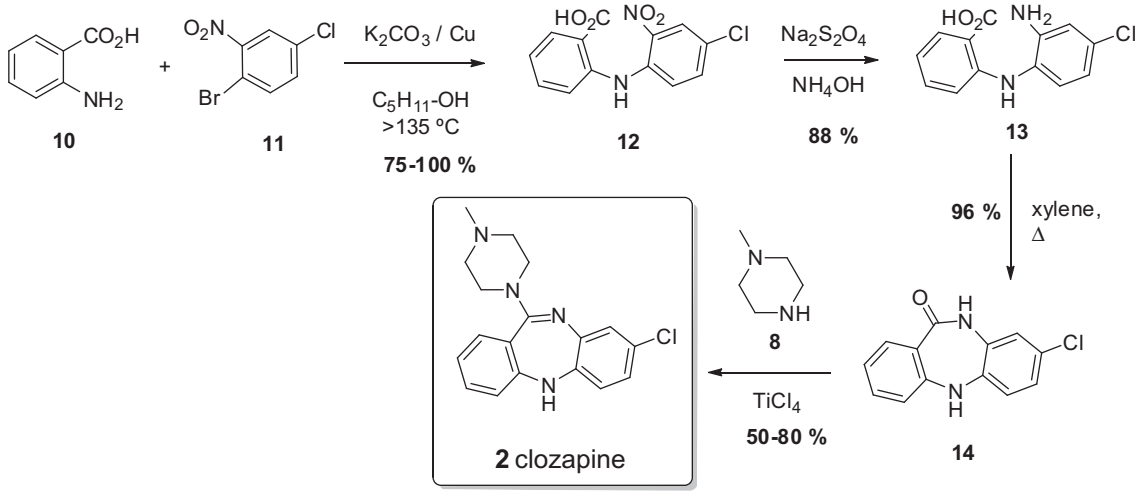
Entry	Metal/Support	Si/Al molar ratio	**1** (%)	**9** (%)	Others (%)
1	Pt^{IV}/Al–MCM-41	15	10	64	26
2	Pt^{IV}/ITQ-2	25	44	40	16
3	**Pt^{IV}/ITQ-2**	**50**	**60**[a]	**26**	**14**

Reaction conditions: **5** (25.9 mg, 0.1 mmol), catalyst (104 mg, 4 mol % metal, activated at 300 °C under vacuum for 3 h), *N*-methylpiperazine (110 μL, 1 mmol), mesitylene (1 mL), H_2 (8–10 bar) in a 2 mL conic double-walled reactor; GC yield unless otherwise indicated.

[a] Isolated yield was 54%.

With this catalytic system, olanzapine **1** could be obtained with 60% yield. This result, though could certainly be improved, is already better than the one reported in patents for the industrial process. It is noteworthy remarking several issues of this new synthesis: (a) chemoselective hydrogenation is achieved with low excess (10 equiv of H_2), (b) Pt^{IV}/ITQ-2 catalyzes the transamination reaction **7**→**1**, (c) mineral acids and bases are avoided and (d) energy intensification has also been carried out since three reaction steps with the corresponding separations have been replaced by a one-pot tandem process.

In order to see if the catalytic system presented here could be generalized for other substrates, we have also performed the synthesis of clozapine **2**, another important antipsychotic.



Scheme 4. Industrial syntheses of clozapine **2**.

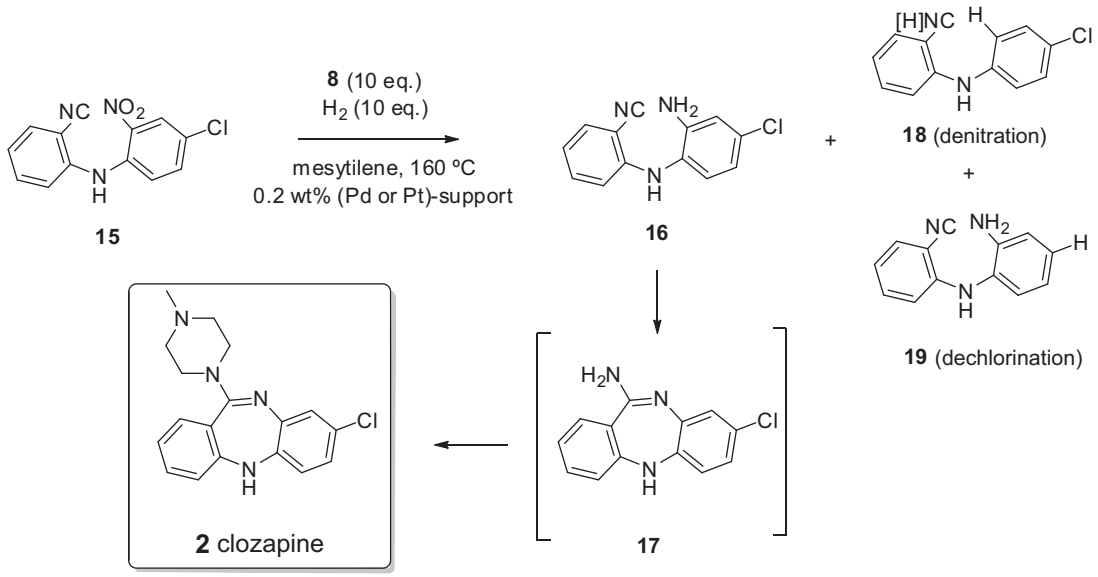
2.2. Clozapine

The most common syntheses for clozapine **2** are shown in Scheme 4.[19,20] As for olanzapine **1**, the synthetic route is based on homogeneous catalysts, in particular on the use of $TiCl_4$. The chemoselective reduction of the nitro group is accomplished by using $Na_2S_2O_4$ in basic media after dibenzylamine **12** is produced by a Buchwald–Hartwig type-coupling. Later cyclisation and $TiCl_4$-catalysed imine formation leads to clozapine **2** in overall yields of ~50% from **12**.

We have applied the same strategy previously used for the synthesis of olanzapine **1**, namely the one-pot synthesis using a bifunctional solid catalysts (Scheme 5). There, we start from derivative **15**, which is easily formed according to a reported procedure.[20] Results obtained are shown in Table 5.

tested under these modified reaction conditions and **2** was obtained in 20% yield (entry 5). The amount of the amine **8** can be lowered (entry 11), although a decrease in the yield of **2** is observed. Finally, **2** was obtained in good yields after prolonged reaction time (entries 7 and 8), using Pt^{IV}/ITQ-2 (Si/Al 50) as catalyst. As it occurs for the synthesis of olanzapine **1**, Pt/Al–MCM-41 was a more active catalyst (compare entries 5 and 9) for the synthesis of clozapine **2**, although less selective giving >50% of by-products.

In order to expand the reaction sequence, the synthesis of **15** by the Buchwald–Hartwig coupling of the corresponding aromatic precursors was attempted, using Cu-supported solid as catalysts (since Pd hampers the subsequent steps). If this would work, a Cu–Pt-supported solid catalyst may ultimately give the whole sequence. Unfortunately, results were fruitless. Therefore, we stay on the one-pot process on a bifunctional solid catalyst that already affords some higher yields of clozapine **2** that the conventional process that requires three steps and the use of homogeneous mineral acids.



Scheme 5. Proposed one-pot synthesis of clozapine **2**.

Table 5
One-pot synthesis of clozapine **2** using bifunctional solid catalysts.

Entry	Metal/Support	Si/Al molar ratio	Reaction Time (h)	H_2 (h)	**2** (%)	**16** (%)	**18** (%)	**19** (%)
1	Pt^{IV}/ITQ-2	50	48	24	2	—	98	—
2	Pd^0/TiO_2	—	18	2	4	91	—	5
3	Pd^0/TiO_2[a]	—	18	2	—	5	22	72
4	Pt^0/TiO_2	—	48	0.5	10	68	11	—
5	Pt^{IV}/ITQ-2	50	48	0.5	20	65	—	—
6	Pt^{IV}/ITQ-2[b]	50	48	0.5	14	55	—	—
7	Pt^{IV}/ITQ-2	50	96	0.5	32	43	—	—
8	**Pt^{IV}/ITQ-2**	**50**	**168**	**0.5**	**55**	**5**	**4**	—
9	Pt^{IV}/Al–MCM-41	15	48	0.5	30	17	28	—
10	Pt^{IV}/ITQ-2	15	48	0.5	20	70	—	—

Reactive amounts: **15** (27.4 mg, 0.1 mmol), catalyst (105 mg, 2 mol % metal), *N*-methylpiperazine (110 μL, 1 mmol), mesitylene (1 mL), H_2 (8–10 bar) in a 2 mL conic double-walled reactor; GC yield unless otherwise indicated; conversion is 100%, rest of material are unidentified products.

[a] 2 wt % Pd (ten times Pd mol% in reaction).

[b] 3 equiv of *N*-methylpiperazine.

Denitration of **15** was the very main product observed with Pt^{IV}/ITQ-2 (Si/Al 50) as catalyst after prolonged hydrogenation (entry 1). Changing to TiO_2-based chemoselective reduction catalysts[18] (entries 2–4) results were improved but the reaction did not go further from **16** (see Scheme 5 and entries 2 and 4 in Table 5) or dechlorination was observed instead (entry 3), which is in accordance with the ability of Pd to insert across aromatic *C*-halogen bonds. It was found that reduction of **15** is fast and can be completed in 30 min using Pt as metal (entry 4). Thus, Pt^{IV}/ITQ-2 (Si/Al 50) was

2.3. Leaching tests

The assessment of the amount of metal dissolved in the medium under reaction conditions (leaching) is crucial since, if so, progressive loss of metal through reuses will occur and, moreover, the catalytic activity could come from the dissolved species rather than

from the solid. We tested independently two of the catalytic solids, Pd^0/TiO_2 and Pt^{IV}/ITQ-2, for the one-pot synthesis of **1** and **2**, respectively.

As we mentioned above (see Table 2, entry 14), Pd^0/TiO_2 was recovered and reused for obtaining **1**. The ICP-AES analysis of the combined filtrates showed some leaching of Pd from the solid (~10 wt %). Thereafter, kinetics experiments were accomplished in order to estimate if the catalytic activity comes from the supported metal or from active species in solution (Fig. 3).

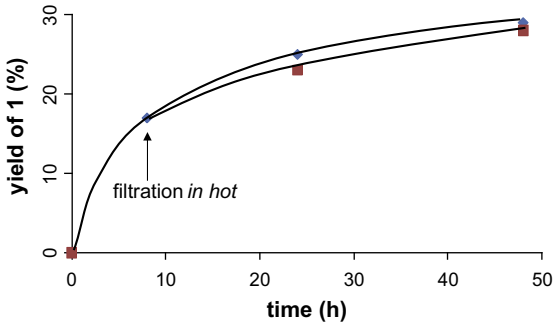


Figure 3. Leaching test: yield of olanzapine **1** when using Pd^0/TiO_2 (0.05 wt %, 0.5 mol %) as catalyst under typical conditions (see Table 2).

As it can be seen, the most of the activity comes from active species in solution. In accordance, when the solid acid and the metal were added separately under optimised conditions (see Table 4, entry 3; ITQ-2 Si/Al 50, and H_2PtCl_6, 4 mol %), both **1** and the by-product **9** were formed in similar yields (60 and 25%, respectively) to those obtained with the bifunctional solid catalyst. Thus, the optimum catalytic system for clozapine **2** was also studied (entry 8, Table 5). The ICP-AES value of metal in solution after reaction was 4.5 wt % (of the original amount added) and the corresponding kinetics experiments are shown in Figure 4.

The study of leaching for **2** revealed that ~25% of the catalytic activity comes from active species in solution, significantly less than for **1**. Although this effect could be related with the depletion of activity of the solid throughout the reuses, the ICP-AES analyses of the catalytic solid after three uses revealed that the loss of Pt was 5% and the Pt content of isolated clozapine **2** was ~4 ppm (ICP-AES), which is below the limit allowed by legislation. Therefore, the catalytic system for **2**, although showing some leaching, could be considered as a truly heterogeneous system in which the metal is preserved onto the solid throughout the uses, in contrast to Pd^0/TiO_2 for **1**.

2.4. Mechanism

A plausible mechanism of the one-pot formation of olanzapine **1** and clozapine **2** over the metal-supported on acid solids is depicted in Scheme 6.

According to this proposal, a chemoselective hydrogenation of the nitro group allows the subsequent attack of the so-formed amine to the acid-activated cyano group, to form the benzodiazepine ring. Finally, an acid-catalysed transamination process with **8** gives the product, **1** or **2**. In the case of **1**, H_2O competes as final nucleophile to give the corresponding amide **9**.

3. Conclusions

The syntheses of olanzapine **1** and clozapine **2** have been accomplished in one-pot by using exclusively heterogeneous solid catalysts. The results reported here constitute a first-step towards the design of an efficient and environmentally-friendly synthetic procedure for benzodiazepines, including olanzapine and clozapine. The nature of the acid sites on the solid and/or its morphology determines the activity and selectivity of the catalyst. Studies on the reusability of the solid catalysts are currently underway.

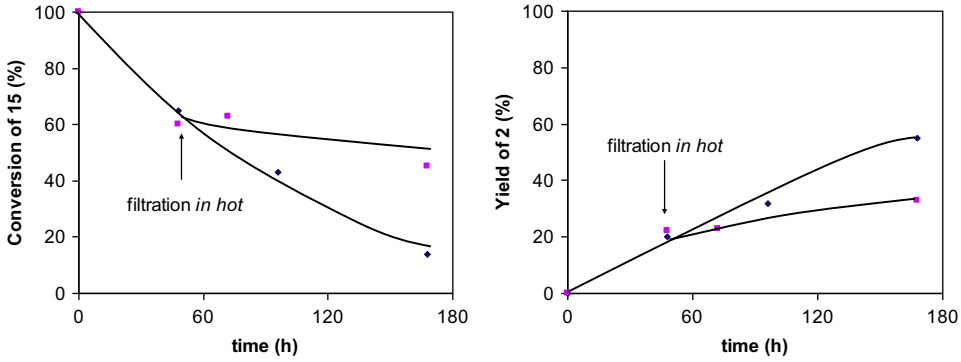
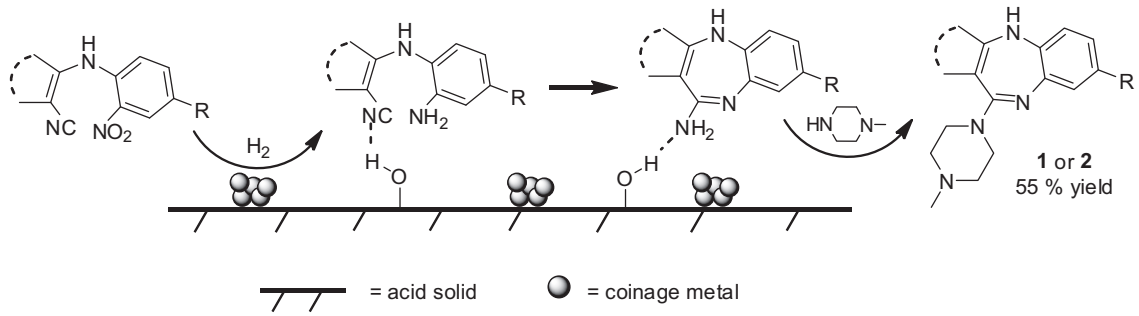


Figure 4. Leaching test: plot-time conversion of **15** (left) and yield of clozapine **2** (right) when using Pt^{IV}/ITQ-2 as catalyst under typical conditions (see Table 5).



Scheme 6. Plausible pathway for the one-pot formation of **1** and **2** over the metal-decorated acid solids used in this work.

4. Experimental

4.1. Typical reaction procedure for olanzapine 1 (entry 8, Table 1)

Pt^{IV}/ITQ-2 (0.4 wt %, 105 mg, 4 mol %) and 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile **5** (25.9 mg, 0.1 mmol) were placed in a hydrogenator reactor. Mesitylene (1 ml) and *N*-methylpiperazine (110 μl, 1 mmol, 10 equiv) were added and the reactor was sealed, purged three times with H_2 and finally loaded with with H_2 (8–10 atm, ~1.0–1.3 mmol, 10–13 equiv). The reaction mixture was placed in a pre-heated oil bath at 160 °C and magnetically stirred for 16 h. After cooling, the hydrogen gas was removed and the mixture was magnetically stirred for additional 32 h at 160 °C. After cooling, the catalyst was filtered off and washed with DCM. The resulting combined filtrates were concentrated under reduced pressure and analysed by NMR. The crude was purified by preparative TLC on silica (10% MeOH in DCM) to afford olanzapine **1** (16 mg, 0.054 mmol, 54%). The spectral data correlates those reported previously.[12] R_f (10% MeOH in DCM): 0.36. GC–MS (*m*/*z*): 312 ($M^{+\bullet}$, 30%), 311 (100%), 310 (70%), 283 (17%), 194 (100%), 103 (93%), 77 (64%). ^{1}H NMR (*δ*, ppm; *J*, Hz): 7.01 (1H, td, *J*=7.9, 1.7), 6.95 (1H, dd, *J*=7.9, 1.5), 6.87 (1H, td, *J*=7.9, 1.7), 6.60 (1H, dd, *J*=7.8, 1.5), 6.30 (1H, q, *J*=1.3), 4.96 (1H, br s), 3.54 (4H, t, *J*=5.0), 2.52 (4H, t, *J*=5.0), 2.36 (3H, s), 2.31 (3H, d, *J*=1.1). ^{13}C NMR (*δ*, ppm): 160.7, 157.5, 142.7, 137.9, 139.4, 128.1, 126.9, 124.7, 124.3, 122.8, 119.1, 54.7 (2C), 46.6 (2C), 45.7, 15.5. HRMS (ESI) [$M+H^+$; calculated for $C_{17}H_{21}N_4S$: 313.1487] found *m*/*z* 313.1485.

4.2. Typical reaction procedure for clozapine 2 (entry 10, Table 3)

A similar procedure to that of olanzapine was employed but using (4-chloro-2-nitrophenyl)-(2-cyanophenyl)-amine **15** (27.4 mg, 0.1 mmol) as substrate, the hydrogen gas was removed after 30 min and the mixture was left to react for 7 days. After filtration, the crude was analysed by GC and purified by preparative TLC on silica to achieve clozapine **2**. The spectral data fits those of the commercial pure compound. R_f (10% MeOH in AcOEt): 0.12. ^{1}H NMR (*δ*, ppm; *J*, Hz): 7.31 (1H, td, *J*=7.6, 1.5), 7.25 (1H, dd, *J*=7.5, 1.6), 7.06 (1H, d, *J*=2.4), 7.02 (1H, td, *J*=7.8, 1.1), 6.84 (1H, dd, *J*=8.3, 2.5), 6.82 (1H, dd, *J*=7.9, 0.8), 6.62 (1H, d, *J*=8.3), 4.91 (1H, s), 3.60 (4H, br s), 2.68 (4H, br s), 2.46 (3H, s). ^{13}C NMR (*δ*, ppm): 169.9 (C), 152.8 (C), 143.5 (C), 140.3 (C), 132.1 (CH), 130.2 (CH), 129.1 (C), 126.8 (CH), 123.5 (C), 123.2 (CH), 123.0 (CH), 120.1 (CH), 120.0 (CH), 54.2 ($CH_2\times2$), 46.9 ($CH_2\times2$), 29.7 (CH_3). HRMS (ESI) [$M+H^+$; calculated for $C_{18}H_{20}N_4Cl$: 327.1376] found *m*/*z* 327.1341.

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Supplementary data

Additional schemes, general methods, reaction procedures, compound characterisation, DRX data for compound **6** and NMR spectra. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.08.022. These data include MOL files and InChiKeys of the most important compounds described in this article.

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