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Multisite Solid Catalyst for Cascade Reactions: The Direct Synthesis of Benzodiazepines from Nitro Compounds

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Abstract: Substituted 1,5-benzodiazepines are selectively synthesized in one pot from substituted nitroaromatics and ketones. The reaction is performed in the presence of hydrogen and in the absence of solvent by using a bifunctional solid catalyst with a chemoselective hydrogenation functional group capable of reducing the nitro group to a diamino group and an acid functional group, which catalyzes the cyclocondensation of the amino group with the ketone.

Keywords: benzodiazepines · cascade reactions · molecular sieves · multisite catalysts · reduction

Introduction

Benzodiazepines and their polycyclic derivatives are an important class of bioactive compounds that are prescribed as tranquilizers, as well as anticonvulsant, antianxiety, analgesic, antidepressive, hypnotic, and anti-inflammatory drugs.[1] More recently the use of 1,5-benzodiazepines has been extended to various diseases such as cancer, viral infection, and cardiovascular disorders.[2]

Commonly, 1,5-benzodiazepines are prepared by cyclocondensation of *o*-phenylenediamine with α,β,-unsaturated carbonyl compounds,[3] β-haloketones,[4] or ketones in the presence of Lewis acids and transition-metal salts as catalysts. Among them, the condensation of *o*-phenylenediamine with ketones in the presence of Brønsted or Lewis acids is the most widely used method for preparing 1,5-benzodiazepines. Many homogeneous catalysts, which sometimes need to be used in lager amounts, have been reported for this condensation. Accordingly, BF_3–etherate,[5] $NaBH_4$,[6] $Yb(OTf)_3$, $Ga(OTf)_3$,[7] polyphosphoric acid,[8] ceric ammonium nitrate,[9] $ZrCl_4$,[10] acetic acid under microwave irradiation,[11] nitrobenzoic acid,[12] and ionic liquids,[13] among others, have been used with variable success. Unfortunately, many of the synthesis methods reported also catalyze the formation of several side products, involve long reaction times, give low yields, or use expensive reagents. Besides these inconveniencies, the use of the catalysts described above requires the neutralization of the acid while producing undesired waste. To avoid that, different heterogeneous acid catalysts such as sulfated zirconia,[14] $AlPW_{12}O_{40}$,[15] clay-supported heteropoly acids,[16] clinoptylolite-type zeolite adsorbents,[17] and zeolites[18] (Heulandite, HY, ZSM-5) have been used for preparing 1,5-benzodiazepines starting from *o*-phenylenediamines, and, in most cases, the cyclocondensation between *o*-phenylenediamine and the ketone requires catalyst-to-phenylenediamine mass ratios of between 2.5 and 5.

Since nitroaromatics are first hydrogenated into the corresponding amines, which can be condensed with ketones in a second step,[19] it appeared to us that it would be of interest to design a multisite solid catalyst and a process capable of producing 1,5-benzodiazepines directly from substituted nitroaromatics and ketones through a cascade reaction. In the first step the nitroaromatics would be chemoselectively hydrogenated with hydrogen in the presence of the ketone on the hydrogenation sites, while in a one-pot consecutive step the cyclocondensation between the aromatic amine and the ketone would occur on the acid sites of the catalyst (Scheme 1). Notice that in this synthesis process there are two critical issues: 1) the selective reduction of the nitro group in the presence of the carbonyl, and 2) the avoidance of the hydrogenation of the imine group in the 1,5-benzodiazepine product. We will show here that the cascade reaction gives a variety of 1,5-benzodiazepines with yields of the order of 90% under very mild conditions (65 °C, 7 bar hydrogen, and a reaction time of 1.5 h). For doing this we have optimized the two catalytic functions, that is, the acid and the hydrogenation.

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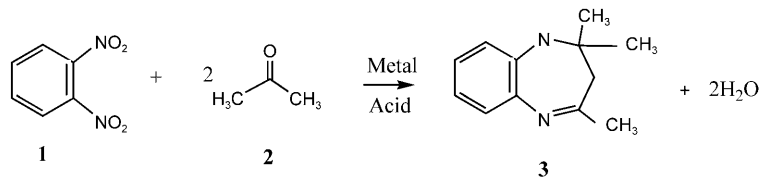


Scheme 1. One-pot process for the synthesis of benzodiazepines.

Results and Discussion

In the case of the acid function, aluminosilicate molecular sieves were selected since with these materials the number and strength of the acid sites can be controlled by modifying the framework Si/Al ratio and molecular sieve structure, while the pore diameter and topology of the catalyst could be adapted to the size of reactants and products. In the case of 1,5-benzodiazepines, the relative large size of the product led us to select three different aluminosilicate molecular sieves as acid catalysts, that is, a large-pore zeolite with a high Si/Al ratio (Beta), a delaminated zeolite (ITQ-2),[20] with a large external surface area, and a structured mesoporous aluminosilicate (MCM-41), as potential candidates to catalyze the cyclocondensation reaction. The characteristics of the solid acid catalysts are given in Table 1.

Table 1. Physicochemical characteristics of the catalysts.

Catalyst	Si/Al	150 °C		BET Surface area
		B[a]	L[a]	[$m^2 g^{-1}$]
Beta	13	60	78	666
ITQ-2	14	28	67	850
MCM-41(14)	12	13	47.9	890
MCM-41(28)	28	16	30.3	940
MCM-41(50)	50	5.7	13.9	1040
MCM-41(80)	80	6.9	11.9	1050

[a] B and L stand for the intensity of the IR band in a.u. of pyridine remaining adsorbed on Brønsted (pyridinium ions) or on Lewis acid sites, after desorption at 150 °C and 10^{-4} Torr.

Two mechanism have been proposed for the synthesis of 1,5-benzodiazepines starting from phenylenediamines and ketones. The first one involves the aldol condensation of the ketone giving the corresponding α,β-unsaturated carbonyl compound, followed by reaction with the amine and cyclization to give the corresponding 1,5-benzodiazepines[5] (Scheme 2A). As suggested by one of the referees the first intermediate in Scheme 2A could also be formed by a monoenamine from diaminobenzene with the ketone and a second molecule of this ketone. In an alternative mechanism it has been proposed[16] that the carbonyl group of the ketone is protonated and reacts with the amine group to give the corresponding imine (see intermediate imine **I** in Scheme 2B). Then, the intermediate imine attacks the carbonyl group of a second activated ketone giving diimine **II** and water. Finally a 1,3 shift of the hydrogen atom attached to the methyl group occurs to form an isomeric enamine (**III**), which cyclizes rapidly yielding the seven-membered benzodiazepines ring (Scheme 2B).

Kinetic results obtained with the molecular sieve MCM-41 catalyst (Figure 1) clearly show the formation of the imine **I** as a primary unstable product, indicating that with this type of catalyst the second mechanism described above is the most probable one. As observed in Table 2, the catalyst activity follows the order MCM-41 > ITQ-2 > Beta. Interestingly MCM-41, with the lowest amount and strength of acid sites (see Table 1), is not only the most active but also gives the highest selectivity to 1,5-benzodiazepine.To explain this behavior one has to take into account the adsorption–desorption properties of the material. Indeed, if we consider that the reactant (1,2-phenylenediamine), the intermediate (imine), and the product (1,5-benzodiazepine) have basic character, the presence of stronger acid sites on the crystalline than on the amorphous molecular sieve[21] will produce a stronger adsorption of the intermediate and final product on Beta and ITQ-2, which will strongly compete with the adsorption of the ketone on the active sites. That stronger adsorption of reactant and product will be responsible for a

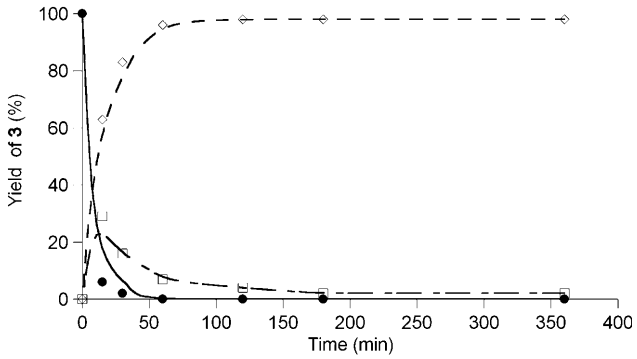


Figure 1. Kinetic curves of the different compounds during the cyclocondensation of *o*-phenylenediamine with acetone using MCM-41 (14) as a catalyst: (●) *o*-phenylenediamine, (◇) benzodiazepine (**3**), and (□) imine **I**.

Table 2. Cyclocondensation between 1,2-phenylenediamine and acetone in the presence of different acid catalyst.[a]

Catalyst	r^o 10^3 [$mol\,min^{-1}\,g^{-1}$]	Yield of **3** [%]	Yield of imine (**I**) [%]	Selectivity [%]
Beta	0.8	91	9	91
ITQ-2	1.1	95	5	95
MCM-41(14)	1.7	97[b]	3[b]	97[b]

[a] Reactions conditions: Diamine (2 mmol), acetone (40 mmol), catalyst (50 mg), at 65 °C, 6 h. [b] Reaction time of 3 h.

lower reaction rate and faster catalyst deactivation with Beta and ITQ-2 than with MCM-41. Therefore, an optimum for the cyclocondensation reaction is achieved with a solid catalyst with structured mesoporous and mild acidity (MCM-41(14)).

In a second step the acidity of the selected mesoporous MCM-41 material was optimized by changing the framework Si/Al ratio while keeping constant the pore diameter. The results obtained (Table 3) show that while the initial reaction rate decreases when decreasing the Al content, it is possible to achieve up to 99% yield of the desired product with an MCM-41 material with a Si/Al ratio of 80. These results suggest that the cyclocondensation reaction does not require strong acid sites and even silanol groups may carry out the reaction, though at a slower rate than the bridging hydroxyl groups of the aluminosilicate. This was indeed confirmed by performing the reaction with pure silica MCM-41 (see results with MCM-41-PS in Table 3).

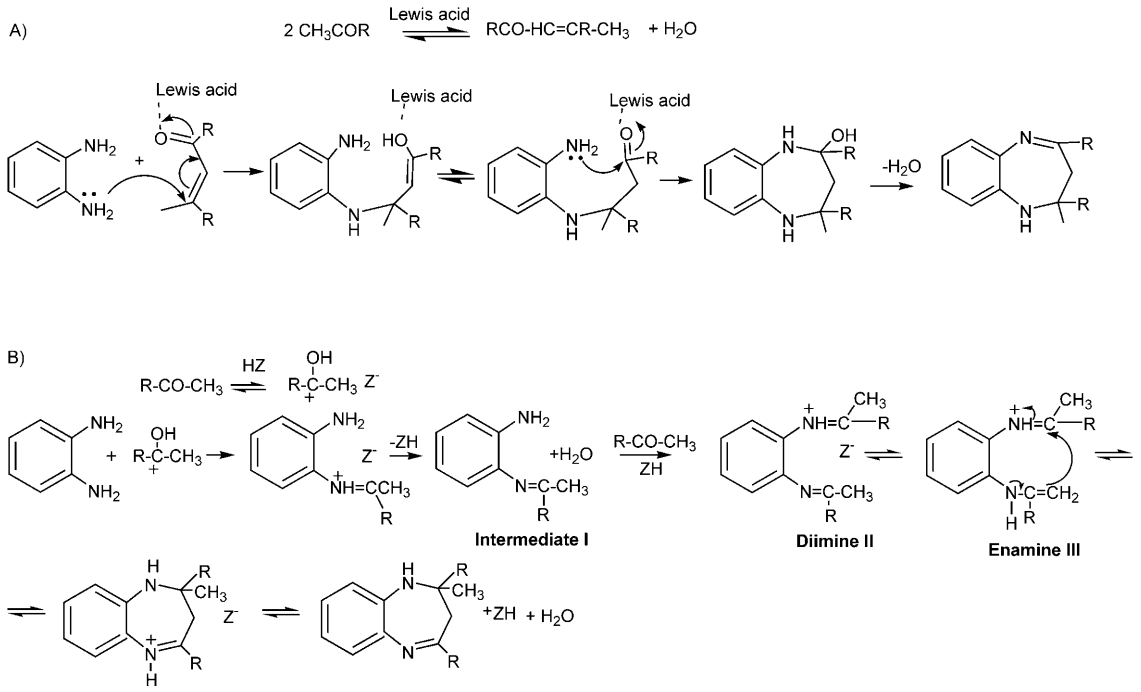
Table 3. Results of cyclocondensation between 1,2-phenylenediamine and acetone using MCM-41 catalyst with different Si/Al ratio.[a]

Catalyst	$r^o\ 10^3$ [mol min^{-1} g^{-1}]	TOF[b] [min^{-1}]	Yield of **3** [%]	Yield of imine (**I**) [%]
MCM-41(14)	1.7	25	97 (3 h)	3 (3 h)
			97 (6 h)	3 (6 h)
MCM-41(28)	1.6	46	96 (3 h)	4 (3 h)
			98 (6 h)	2 (6 h)
MCM-41(50)	1.3	64	92 (3 h)	8 (3 h)
			96 (6 h)	4 (6 h)
MCM-41(80)	1.3	111	91 (3 h)	9 (3 h)
			99 (6 h)	1 (6 h)
MCM-41-PS	0.4	–	76 (6 h)	20 (6 h)

[a] Reactions conditions: Diamine (2 mmol), acetone (40 mmol), catalyst (50 mg), at 65 °C, 6 h. [b] Calculated as r^o/([Al]/[Al+Si]).

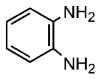
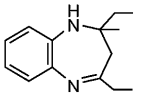
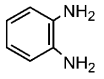
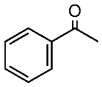
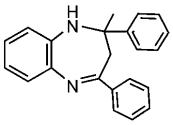
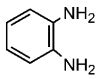
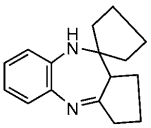
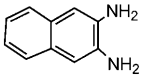
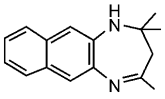
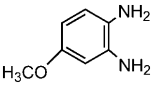
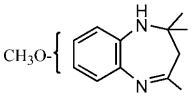
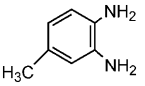
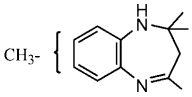
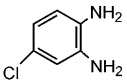
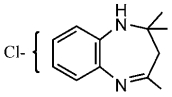
The mesoporous catalyst can be recycled simply by washing the MCM-41 with acetone, and only a 3% decrease in yield (96% yield for a reaction time of 6 h) has been observed after four catalyst recycles. The generality of the MCM-41 catalyst for producing benzodiazepines starting from phenylenediamines has been explored by reacting different ketones and different 4-substituted 1,2-phenylenediamines (Table 4). With an unsymmetrical aliphatic ketone (2-butanone) only one regioisomer (2,3-dihydro-1*H*-1,5-benzodiazepine (**4**)) was obtained, indicating that ring closure occurs selectively from one side of the carbonyl group. High yields of the desired product are also observed with cyclic (cyclopentanone) and aromatic substituted ketones (acetophenone). When diamines with electron withdrawing (Cl) or donating (CH_3, OCH_3) groups are reacted, a mixture of the corresponding regioisomers 7- and 8-substituted 1,5-benzodiazepines are obtained in a 1:1 molar ratio. The presence of electron-donating groups in the diamine ring increases the yield and rate of formation of 1,5-benzodiazepine (Table 4, entries 5 and 6), while electron withdrawing groups decrease the reactivity (Table 4, entry 7). The decrease in reactivity is larger when there is a fused aromatic ring to the diamine (Table 4, entry 4).

Multisite catalyst: the cascade reaction: As mentioned above the final objective of the work was to find a multisite selective catalyst that allows one to produce 1,5-benzodiazepines directly from nitroaromatics and ketones by means of a cascade reaction in which the selective hydrogenation of



Scheme 2. Possible mechanisms for the formation of 1,5-benzodiazepines.

Table 4. Synthesis of different 1,5-benzodiazepines using MCM-41(14) as acid catalyst.[a]

Entry	Diamine	Ketone	Product	T [°C]	t [h]	Yield[c] [%]
1[b]			 **4**	95	4	93 (95)
2[b]			 **5**	100	2	94 (95)
3[b]			 **6**	100	1	100 (100)
4			 **7**	65	14	73 (73)
5			 **8**	65	2	98(98)
6			 **9**	65	2	96 (96)
7			 **10**	65	4	96 (96)

[a] Reactions conditions: Diamine (2 mmol), acetone (40 mmol), catalyst (50 mg), at 65 °C, 6 h. [b] Diamine (2 mmol), ketone (10 mmol). [c] Selectivity in brackets.

the nitro groups to form the aromatic amines is followed by a cyclocondensation reaction between the diamines and ketones. Since we have already seen that MCM-41 is an active and selective catalyst for the cyclocondensation reaction under very mild reaction conditions (65 °C), we need a hydrogenation catalyst capable of reducing, at low temperature (65 °C), the dinitroaromatic without reducing the carbonyl group of the ketone nor the C=N double bound in the benzodiazepines. We have recently found[22] that nanocrystals of Pt decorated with TiO_x are able to selectively reduce the nitro groups in a large variety of substituted nitroaromatics under mild reaction conditions owing to the effect of Pt coverage by TiO_2 on the preferential adsorption of the nitro versus the double bond or carbonyl group.[22] The catalyst can be prepared by supporting nanosized crystals of Pt on TiO_2 and decorating the exposed (111) and (110) Pt crystal faces with TiO_2 from the support by means of a simple activation at 450 °C in the presence of hydrogen. Taking this into account we have prepared a composite catalyst by combining 0.2 wt % Pt/TiO_2, and MCM-41 for carrying out the direct transformation of dinitrobenzene plus a ketone into the corresponding benzodiazepine. The kinetic curves in Figure 2 show the formation of 2-nitroaniline, 1,2-phenylenediamine, the imine intermediate, and finally the corresponding benzodiazepine.

The behavior of the kinetic curves allows us to write a reaction scheme (Scheme 3) in which in a first hydrogenation step the 2-nitroaniline (**A**) is formed and this reacts more slowly with hydrogen to produce the 1,2-phenylenediamine (**B**). Product (**B**) is observed in minor amounts because it quickly reacts with the ketone to give the imine (**C**), which is detected, while we have not detected the imine intermediate (**D**) coming from the condensation of the amino group of 2-nitroaniline and the ketone.

Notably, under these reaction conditions it is possible to convert dinitrobenzene quantitatively and with 94 % selectivity to the benzodiazepine. However, if the reaction is continued in the presence of

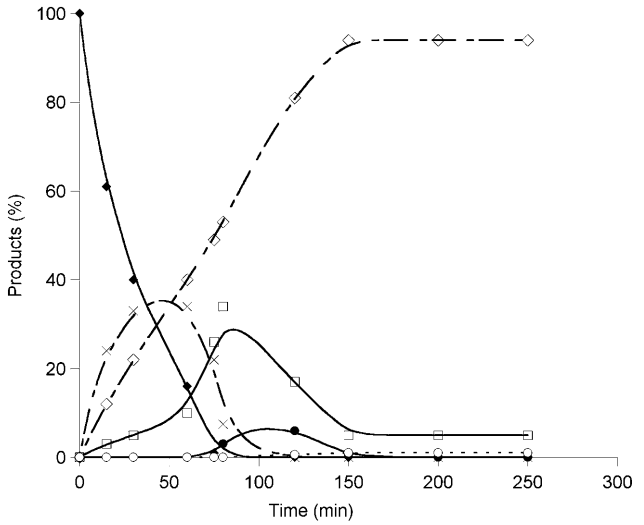
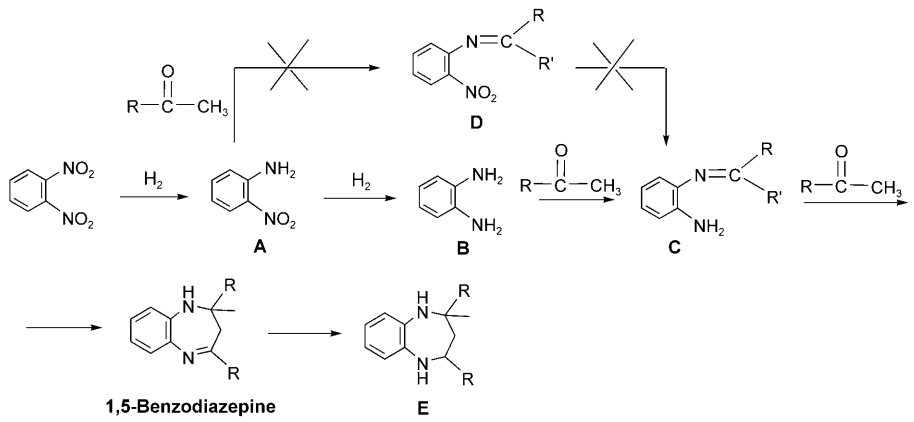


Figure 2. Kinetic curves of the different compounds during the one-pot hydrogenation–cyclocondensation sequence of 1,2-nitrobenzene and acetone in the presence of Pt/TiO_2-MCM-41(14). (◆) 1,2-dinitrobenzene, (●) 1,2-phenylenediamine B (□) imine C, (x) 2-nitroaniline A, (○) product **E**, (◇) 1,5-benzodiazepine (**3**).

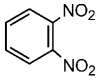
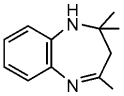
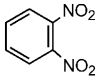
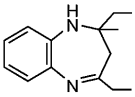
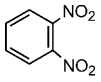
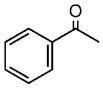
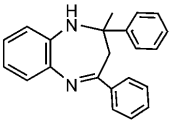
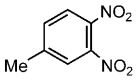
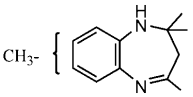
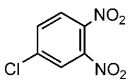
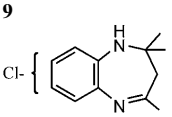
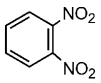
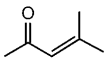
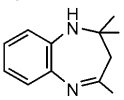


Scheme 3. Reaction scheme for the one-pot hydrogenation–cyclocondensation sequence.

hydrogen when the nitro groups have been fully converted, it is possible to detect minor amounts of the product **E** due to hydrogenation of the C=N double bound of the benzodiazepine.

The composite catalyst works with a series of dinitroaromatics and ketones, while solvent is not required. By adjusting the reaction conditions, 1,2-dinitrobenzene reacts selectively with various ketones (see Table 5). 4-Aryl-substituted dinitro compounds also react selectively with acetone producing a mixture of the corresponding 7- and 8- substituted 1,5-benzodiazepines regioisomers in a 1:1 molar ratio. In both cases complete conversion and similar selectivities were observed (see Table 5). In the case of entry 4 (Table 5), 3% of the corresponding 2,3,4,5-tetrahydro-1,5-benzodiazepine (compound **E** in Scheme 3) and 7% of the imine intermediate (**C**) were also formed. When 1-chloro-3,4-nitrobenzene and acetone were allowed to react (entry 5, Table 5), 10% of imine intermediate was also formed. Finally, reaction with an α, β-unsaturated ketone (entry 6, Table 5 < xtabr5), gives excellent conversion and selectivity. In general conversions above 90% with selectivities of the order of 90% have been obtained in the cases studied here by using the composite catalyst formed by the decorated 0.2 wt% Pt/TiO_2 and MCM-41. It should be remarked that if commercial 5 wt% Pt/C, Pt/Al_2O_3, Pt/C, or

Table 5. Synthesis of different 1,5-benzodiazepines using 0.2 wt% Pt/TiO_2-MCM-41(14) as catalysts.[a]

Entry	Dinitroaromatic	Ketone	Product	P [bar][b]	$T_{hydrog.}$ [°C]	$t_{hydrog.}$ [h]	$T_{reaction}$ [°C]	t_{total} [h]	Conversion [%][c]	S [%][c,d]
1			 **3**	7	55	1.25	65	2.5	100	94
2			 **4**	7	65	1	95	4	92[e]	89
3			 **5**	10	65	7	100	10	95[f]	84
4			 **9**	7	55	1.25	65	3.25	100	90
5			 **10**	7	55	1.75	65	3.75	100	90
6[g]			 **3**	10	65	3	65	10	95[f]	95

[a] Reaction conditions: Dinitroaromatic (0.8 mmol), ketone (1.3 mL), 0.2 wt% Pt/TiO_2 (60 mg), MCM-41(14) (30 mg). [b] Reactions were performed under isobaric conditions. [c] Calculated by CG using *o*-xylene as internal standard. [d] Selectivity (%). [e] 2-Nitroaniline was detected in 7% yield. [f] 2-Nitroaniline was detected in 5% yield. [g] Without MCM-41catalyst.

undecorated Pt/TiO_2 (reduced at 200 °C) together with MCM-41 (see Table 6) are used as catalysts, complete conversions are obtained but selectivities to the 1,5-benzodiazepines are lower.

Since Au/TiO_2 is also a chemoselective catalyst for the hydrogenation of nitroaromatic compounds,[22,23] thought at higher temperatures than decorated Pt, we have carried out the reaction with an Au/TiO_2–MCM-41 composite catalyst at 120 °C. The results given in Table 6 (entry 8) show that the composite Au/TiO_2–MCM-41 also allows the reaction with good selectivity but a higher reaction temperature is required.

Finally we have tested if the acidity of the TiO_2 was sufficient to perform the cyclocondensation when the reaction was carried out at higher temperatures (120 °C) since this would avoid the use of MCM-41. Results in Table 6 (entry 7) show that in this case, longer reaction times are required for full conversion than with the composite catalyst, while the selectivity to the benzodiazepine is much lower owing to the remaining unreacted imine intermediate **C**. It appears then that TiO_2 is not acidic enough to efficiently facilitate the cyclocondensation reaction.

Conclusions

We have shown that it is possible to synthesize 1,5-benzodiazepines directly from substituted nitroaromatics and ketones in high yields in a one-pot system. The reaction is carried out in the presence of hydrogen and without using solvents by means of a bifunctional catalyst that chemoselectively performs the hydrogenation of the nitro group to the amino group, which subsequently cyclocondensates with the ketone on the acid sites of the composite catalyst.

Experimental Section

General: MCM-41 with a Si/Al ratio of 14, 28, 50, and 80, and a pore diameter of 3.5 nm were prepared in accordance with reference [24]. The ITQ-2 delaminated material was synthesized from the corresponding laminar precursor with the MWW structure following reference [20]. Beta zeolite was a commercial sample (Beta-CP811) provided by PQ-Zeolyst. The 0.2 wt% Pt/TiO_2 catalyst was prepared following a recently described procedure.[22] This catalyst was obtained by the incipient wetness technique using H_2PtCl_6 as the platinum precursor. Then, it was reduced under H_2 flow over 3 h at 450 °C before its use in the reaction. The 0.2 wt% Pt/Al_2O_3 and 0.2 wt% Pt/C catalysts were prepared following a known procedure.[22]

Acidity measurements were carried out by adsorption–desorption of pyridine by IR spectroscopy. The IR spectra were recorded on a Nicolet 710 FTIR using self-supported wafers of 10 mg cm^{-2}. The calcined samples were outgassed overnight at 400 °C and 10^{-3} Pa dynamic vacuum; then, pyridine was admitted into the cell at room temperature. After saturation, the samples were outgassed at 250 °C for 1 h under vacuum, cooled to room temperature and the spectra were recorded.

1-Chloro-3,4-dinitrotoluene was commercially available from ABCR GmbH and Co. The rest of the reagents used in this paper including 5 wt% Pt/C were purchased from Sigma–Aldrich Co.

Cyclocondensation reaction procedure: A mixture of *o*-phenylenediamine (2 mmol) with acetone (40 mmol) or derived ketone and nitrobenzene (100 mg) as internal standard was prepared and added onto the catalyst (50 mg) in a batch reactor. The resultant suspension was magnetically stirred and heated at the required temperature in a silicone oil bath with an automatic temperature control system. Samples were taken at regular time periods and analyzed by gas chromatography (GC). At the end of the reaction the catalyst was filtered and washed with acetone, and the organic solution was concentrated under reduced pressure, weighed, and analyzed by ^{1}H NMR spectroscopy (300 MHz Varian VXR-400S) and GC-MS (Hewlet-Packard 5988 A). All compounds are known and spectroscopic data were in good agreement with those reported in the literature.

After the reaction, the catalyst was submitted to continuous solid–liquid extractions with acetone in micro-Soxhlet equipment. After removal of the solvent the residue was also weighed and analyzed by GC-MS. In all experiments the total recovered material accounted for more than 95% of the starting *o*-phenylenediamine.

Cascade reaction procedure: Catalytic reactions were performed in a reinforced glass reactor (2 mL capacity) equipped with a manometer (for

Table 6. Product distribution for the synthesis of 2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3**) using hydrogenation catalysts and MCM-41(14).[a]

Entry	Hydrogenation catalysts	Reduction T [°C]	P [bar][b]	$T_{hydr.}$ [°C]	Tim_{hydr} [h]	$T_{reaction}$ [°C]	t_{total} [h]	Conv. [%][g]	S_a [%][h]	S_b [%][i]	S_c [%][j]	S_d [%][k]
1	0.2 wt% Pt/TiO_2	450	7	55	1.25	65	2.5	100	94	5	1	–
2	0.2 wt% Pt/TiO_2	200	7	55	1	65	3	100	77	14	6	3
3	0.2 wt% Pt/Al_2O_3	450	7	55	1	65	3	99	77.5	11.2	10.7	0.7
4	0.2 wt% Pt/C	450	7	55	10	65	10	97	85	2.7	8.2	4.1
5[c]	5 wt% Pt/C	–	7	55	0.5	65	1.5	100	33	41	–	26
6[d]	0.2 wt% Pt/TiO_2 (without MCM-41)	450	7	55	1	85	14	100	75	6	14	5
7[e]	1.5 wt% Au/TiO_2 (without MCM-41)	–	10	120	1.7	120	14	100	73	1	19	8
8[f]	1.5 wt% Au/TiO_2	–	10	120	1.7	120	4	99	93	1	10	–

[a] Reaction conditions: Dinitrobenzene (0.8 mmol), acetone (1.3 mL), hydrogenation catalyst (60 mg), MCM-41(14) (30 mg). [b] Reactions were performed under isobaric conditions. [c] Hydrogenation catalyst (30 mg). [d] Hydrogenation catalyst (120 mg). [e] Hydrogenation catalyst (100 mg). [f] Hydrogenation catalyst (100 mg) and MCM-41 (30 mg). [g] Calculated by CG using *o*-xylene as internal standard. [h] S_a = Selectivity of 1,5-benzodiazepine. [i] S_b = Selectivity of product **E**. [j] S_c = Selectivity of imine C. [k] S_d = Selectivity of other products (entries 2 and 3: 3% and 0.7% of a mixture of two compounds with M_W 190–192, respectively; entry 4: 4.1% of compound with M_W 228; entry 5: 22% of a mixture of two compounds with M_W 190–192 and 4% of another compound with M_W 150; entry 6: 3% hydrogenated intermediate (M_W = 150) and 2% of 1,2-phenylenediamine; entry 7: 8% of 1,2-phenylenediamine).

pressure control) and a capillary tube coupled to a Luer-lock valve through which H_2 can be introduced into the reactor and through which samples can be withdrawn for analysis at after desired period of reaction.

A mixture of the appropriate dinitroaromatic (0.8 mmol) and ketone (1.3 mL) was introduced into the reactor together with a catalytic amount of 0.2 wt % Pt/TiO_2 (60 mg) and MCM-41 (14) (30 mg). *o*-Xylene was used as internal standard in all cases. Afterwards, the reactor was sealed and air was purged by flushing three times with 7 bar of hydrogen. Then, the reaction mixture was magnetically stirred, heated at the selected temperature in a silicone oil bath, and the reactor was pressurized with H_2 at the required pressure. During the hydrogenation reaction, the pressure was maintained constant and the reaction was monitored by gas chromatography. When the hydrogenation reaction was finished, the reactor was depressurized and the reaction temperature was increased. The reaction mixture was then stirred at the required temperature until the reaction was complete. Finally, the catalysts were filtered and the organic solution was concentrated under vacuum and analyzed by GC-MS (Agilent 5973N).

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3):[25] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.11$, 6.96, 6.71 (m, m, m, 1:2:1, 4 CH_{ar}), 2.94 (sa, 1H, NH), 2.34 (s, 3H, N=C-Me), 2.21 (s, 2H, -CH_2), 1.32 ppm (s, 6H, -$C(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.4$ (N=C-), 140.7, 137.9 (C_{qar}), 126.9, 125.5, 122.1, 121.7 (CH_{ar}), 68.4 (NH-C_q), 45.1 (CH_2), 30.5 (-$C(Me)_2$), 29.9 ppm (N=C-*Me*); MS (80 eV): *m*/*z* (%): 188 [M^+], 173 (100), 132 (87), 133 (72), 131 (33), 174 (18), 39 (14), 92 (13), 65 (13), 41 (12).

2,4-Diethyl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (4):[25] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.11$, 6.93, 6.67 (m, m, m, 1:2:1, 4 CH_{ar}), 3.32 (sa, 1H, NH), 2.56 (q, 2H, -CH_2CH_3), 2.15 (m, 2H, -CH_2), 1.58 (m, 2H, -CH_2CH_3), 1.21 (t, 3H, -CH_2CH_3), 1.20 (s, 3H, -CH_3), 0.90 ppm (t, 3H, -CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.8$ (N=C-), 139.8, 136.9 (C_{qar}), 126.0, 124.3, 120.7 (1:1:2, CH_{ar}), 69.7 (NH-C_q), 41.0, 34.6 (CH_2), 25.9, 9.6, 7.5 ppm (CH_3); MS (80 eV): *m*/*z* (%): 216 [M^+], 187 (100), 145 (22), 188 (14), 133 (13), 147 (12), 146 (10), 201 (10), 132 (6), 131 (6).

2-Methyl-2,4-diphenylyl-2,3-dihydro-1*H*-1,5-benzodiazepine (5):[25] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$, 7.29, 7.09, 6.87 (m, m, m, m, 4:7:2:1, 14 CH_{ar}), 3.55 (sa, 1H, NH), 3.09 (dd, 2H, -CH_2), 1.79 ppm (s, 3H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.7$ (N=C-), 147.6, 140.1, 139.6, 138.1 (C_{qar}), 129.7, 128.7, 128.3, 128.0, 127.6, 127.1, 126.4, 125.4 (1:1:2:2:3:1:2:1:1, CH_{ar}), 73.7 (NH-C_q), 43.1 (CH_2), 29.9 ppm (Me); MS (80 eV): *m*/*z* (%): 340 [M^+], 195 (100), 194 (98), 235 (84), 297 (54), 77 (31), 312 (30), 193 (29), 103 (21), 311 (19), 65 (19).

10-Spirocyclopentane-1,2,3,9,10,10a-hexahydrobenzo[*b*]cyclopentane[*e*]-[1,4]diazepine (6):[25] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.39$–6.74 (m, 4H). 4.52 (s, br, NH, 1H), 2.60–2.35 (m, 3H), 1.90–1.32 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.0$, 143.3, 139.8, 132.2, 126.9, 119.5, 118.4, 67.3, 54.5, 39.0, 38.5, 33.4, 28.8, 24.2, 24.1, 23.5 ppm; MS (80 eV): *m*/*z* (%): 240 [M^+].

2,3-Dihydro-2,2,4-trimethyl-1*H*-naphtho(2,3-*b*)[1,4]diazepine (7):[11] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$, 7.62, 7.55, 7.32, 7.13 (m, m, s, m, s, 1:1:1:2:1, 6 CH_{ar}), 3.70 (sa, 1H, NH), 2.40 (s, 3H, N=C-Me), 2.22 (s, 2H, -CH_2), 1.36 ppm (s, 6H, -$C(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.4$ (N=C-), 136.7, 131.0, 129.6, 129.5 (C_{qar}), 126.7, 124.8, 123.1, 122.8, 116.7 (CH_{ar}), 65.0 (NH-C_q), 43.8 (CH_2), 29.1 (-$C(Me)_2$), 28.8 ppm (N=C-*Me*); MS (80 eV): *m*/*z* (%): 238 [M^+], 223 (100), 183 (40), 182 (31), 224 (18), 115 (17), 181 (10), 140 (9), 180 (7), 114 (7).

2,3-Dihydro-7-methoxy-2,2,4-trimethyl-1*H*-1,5-benzodiazepine (8):[11,26] Mixture of regioisomers. ^{1}H NMR (300 MHz, $CDCl_3$,): $\delta = 6.99$, 6.78, 6.59 (m, m, s, 1 H each, 3 CH_{ar}), 3.70 (s, 3H, -OMe), 3.01 (sa, 1H, NH), 2.26 (s, 3H, N=C-Me), 2.15 (s, 2H, -CH_2), 1.29 ppm (s, 6H, -$C(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$,): $\delta = 172.5$ (N=C-), 138.0, 135.2, 131.8 (C_{qar}), 122.7, 122.0, 121.8 (CH_{ar}), 68.4 (NH-C_q), 55.0 (-OMe), 45.1 (CH_2), 30.2, 20.6 ppm (2:1, Me); MS (80 eV): *m*/*z* (%): 218 [M^+].

2,3-Dihydro-2,2,4,7-tetramethyl-1*H*-1,5-benzodiazepine (9):[11,26] Mixture of regioisomers. ^{1}H NMR (300 MHz, $CDCl_3$,): $\delta = 6.91$, 6.76, 6.62 (m, m, s, 1 H each, 3 CH_{ar}), 2.87 (sa, 1H, NH), 2.31 (s, 3H, -Me), 2.24 (s, 3H, -Me), 2.19 (s, 2H, -CH_2), 1.30 ppm (s, 6H, -$C(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$,): $\delta = 171.4$ (N=C-), 141.1, 137.8, 135.3 (C_{qar}), 127.1, 127.0, 126.1 (CH_{ar}), 67.7 (NH-C_q), 45.3 (CH_2), 30.6, 20.9 ppm (2:1, Me); MS (80 eV): *m*/*z* (%): 202 [M^+], 147 (100), 146 (100), 187 (100), 145 (100), 188 (92), 77 (77), 39 (62), 41 (54), 130 (50).

7-Chloro-2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine (10):[11] Mixture of regioisomers. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.99$, 6.88, 6.68 (s, m, m, 1 H each, 3 CH_{ar}), 3.23 (sa, 1H, NH), 2.30 (s, 3H, -Me), 2.21 (s, 2H, -CH_2), 1.29 ppm (s, 6H, -$C(Me)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 172.8 (N=C-), 139.2, 138.5, 130.3 (C_{qar}), 128.3, 121.6, 120.9 (CH_{ar}), 67.7 (NH-C_q), 45.3 (CH_2), 30.6, 30.4 ppm (2:1, Me); MS (80 eV): *m*/*z* (%): 222 [M^+], 207 (100), 166 (50), 167 (48), 209 (32), 168 (20), 169 (14), 165 (13), 208 (13).

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