Fast TiO2-catalyzed direct Amidation of Carboxylic Acids under mild dielectric Heating

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Fast TiO$_2$-catalyzed direct amidation of neat carboxylic acids under mild dielectric heating†

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The development of green protocols for amide bond formation is a major socioeconomic goal for chemical and pharmaceutical industries and an important challenge for academic research. We herein report a protocol for the quantitative conversion of carboxylic acids and amines to form amides at 100 °C in the presence of a TiO$_2$ powder catalyst, under monomodal microwave irradiation. The sustainability of the process appears to be augmented by the ease with which the catalyst is recycled.

1. Introduction

The direct amidation reaction between carboxylic acids and amines is still a difficult task[1] because it requires high temperatures (>180 °C) which are often incompatible with most functionalised molecules.[2,3] Carboxylic acids can be activated towards nucleophilic attack by coupling[4] and stoichiometric reagents,[5,6] forming acid chlorides, anhydrides or esters. The main drawbacks of these time-consuming strategies are the formation of toxic/corrosive by-products, poor atom economy and costly waste streams that clearly mark them out as non-sustainable processes.[7] In recent years, new environmentally benign amide preparation protocols that start with acids and amines have been described. They fundamentally exploit enabling technologies such as microwave (MW) irradiation,[8] efficient heterogeneous catalysis,[9–11] and organocatalysis,[12,13] often in solvent-free conditions.[14] Dielectric heating is a valid response to stubborn, time-consuming reactions[15] and can be applied on a range of scales, from milliliters to kilograms.[16] Many protocols have been developed using homogeneous solid catalysts such as ZrCl$_4$,[17,18] and some nano-sized particles are worthy of note as their high specific surface area gives them high reactivity.[19,20] In particular, titanium dioxide (TiO$_2$)[21] (Evonik P25) is used as a stable, non-volatile, odorless, white powder with a high specific surface area that, as is well known, has received, since a long time ago, a huge interest as a photocatalyst,[22,23] but it can be also exploited for thermal catalysis.[21] Different kinds of TiO$_2$ have been synthesized and applied in amide bond synthesis giving moderate yields even in long reaction times.[24–26] In this piece of work, we describe an efficient protocol for the direct amidation of carboxylic acids in a monomode MW reactor in the presence of a TiO$_2$ catalyst which has supplied a significant increase in the amidation yield while

allowing for a decrease in the reaction temperature over catalyst-free MW processes.[27] The catalyst was furthermore easily recovered from the reaction mixture and recycled after activation, thereby rendering the process economically viable. Finally, as it was recently demonstrated in the vapor phase that carboxylic acids can be activated toward amidation on the surface of an oxide *via* carboxylate formation,[28] an investigation of the interaction of benzoic acid (as it gave the highest yields of the carboxylic acids considered) and the TiO_2 catalyst has been performed.

2. Experimental

2.1. Reagents and equipment

D_2O (99.90% D) was purchased from Euriso-top, and all other solvents and reagents were purchased from Sigma Aldrich, Italy, and used without further purification unless otherwise noted.

The commercial TiO_2 powder P25 (*ca.* 80% anatase, 20% rutile, specific surface area ~50 m^2 g^{-1}, average primary particle size 21 nm), AEROXIDE® (a highly dispersed titanium dioxide manufactured according to the AEROSIL® process), was kindly provided by Evonik Industries and used as the catalyst. The catalyst was used as found or, in some cases, after treatment in a muffle furnace at 450 °C for 1.5 h, to remove molecular species, in particular any of an organic nature, which may have adsorbed onto the surface of the catalyst while it was simply stored in air.[29] This was followed by cooling to room temperature and storage in ambient air before introduction in the reactor.

Reactions were performed in a monomode MW reactor (Monowave 300, Anton Paar, with autosampler MAS24) and in a professional multimode oven (MicroSYNTH – MLS GmbH, Milestone Srl) both equipped with a built-in IR sensor for temperature control.

GC-MS analyses were carried out in a gas chromatograph Agilent 6890 (Agilent Technologies, USA) fitted with a mass detector Agilent Network 5973 using a capillary column that was 30 m long and had an i.d. of 0.25 mm and a film thickness of 0.25 mm. GC conditions were injection split of 1:20, injector temperature of 250 °C, and detector temperature of 280 °C. The gas carrier was helium (1.2 mL min^{-1}), and the temperature program was from 70 °C (2 min) to 300 °C at 5 °C min^{-1}. NMR spectra were recorded on a Bruker Avance 300 (300 MHz and 75 MHz for 1H and 13C, respectively) at 25 °C; chemical shifts were calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH = 7.26, δC = 77.16). HRMS was determined using MALDI-TOF mass spectra (Bruker Ultraflex TOF mass spectrometer).

2.2. Reaction conditions

In the typical amidation procedure, a finely grinded mixture of benzoic acid (150 mg, 1.2 mmol), benzylamine (140 µL, 1.3 mmol, d = 0.98 g L^{-1}), and TiO_2 powder (Evonik P25, 100 mg) was irradiated in an MW monomode reactor in a borosilicate glass tube G30 (30 mL). The reaction mixture was heated to 100 °C (average power: 70 W) for 20 min under stirring (600 rpm), and EtOAc (5 mL) was added. The suspension was centrifuged at 3000 rpm for 3 min to remove the TiO_2 catalyst. The recovered organic phase was poured into a separating funnel and washed with H_2O (3 × 5 mL), with a saturated solution of $NaHCO_3$ (3 × 5 mL), and then with brine (3 × 5 mL). It was finally dried over anhydrous Na_2SO_4 and then evaporated under vacuum which gave the product. Overall

conversion and yield were determined by GC-MS analysis. The structure of the products was confirmed by NMR and mass spectrometry.

2.3. IR spectroscopic measurements

For IR spectroscopic measurements, the TiO_2 powder was pressed into self-supporting pellets ("optical thickness" *ca.* 10 mg cm^{-2}), which were placed in an IR cell equipped with CaF_2 windows and a valve connecting to the vacuum lines (residual pressure 1.0×10^{-5} mbar) allowing thermal treatment and adsorption/desorption experiments to be carried out *in situ*. Samples were heated inside the cell, under dynamic vacuum, from room temperature to 723 K (*ca.* 5 K min^{-1}) and outgassed at this temperature for 1 h. To compensate for the reductive effect on TiO_2 produced by this dehydration/dehydroxylation treatment, 6 mbar of O_2 were admitted into the cell and kept in contact with the samples for 1 h at 723 K. The system was subsequently cooled to 473 K in O_2 and finally to room temperature under outgassing. The treated samples appeared perfectly white, as expected for stoichiometric TiO_2. The cell was then transferred to the IR instruments (Bruker Vector 22; detector: DTGS), without exposing the samples to air and connected to another vacuum line for the *in situ* adsorption/desorption of H_2O, D_2O and C_6H_5COOD vapors. The spectra were collected at beam temperature (*ca.* 50 °C, b.t.) with a resolution of 4 cm^{-1} at 100 scans, to assure a good signal-to-noise ratio.

3. Results and discussion

The MW-assisted direct amidation of benzoic acid (**1**) with benzylamine (**2**) was chosen as the model reaction (Scheme 1) for the optimization of conditions and parameters.
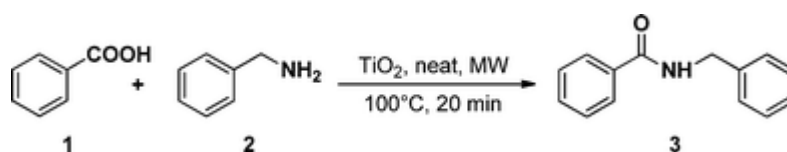
Scheme 1 Solvent-free MW-assisted amidation of benzoic acid.

We initially conducted some tests comparing multimode and monomode MW reactors and observed that the solvent-free conversion of benzoic acid to amide in the presence of TiO_2 was faster and more efficient when irradiated in a monomode cavity (Table 1).[30,31] Quantitative conversion was observed for 20 min under neat conditions at 100 °C, while the reaction did not occur with solvents (toluene or acetonitrile; Table 2). Longer reaction times and higher temperature did not improve reaction rate and yield. As reported in Table 1, at low reaction temperature (up to 80 °C) the catalyst pre-activation step is required for water desorbing on the TiO_2 surface. Otherwise, at 100 °C and over, the higher power density of the monomode MW reactor makes the pre-activation step unnecessary. The high yield at mild reaction conditions is certainly worthy of note as previous catalyst-free protocols require much higher temperatures (200–300 °C), which are often incompatible with many thermo-labile organic moieties, to give their best performance.[27]

Table 1 Benzoic acid (**1**)/benzylamine (**2**) amidation (TiO_2 33.3 wt%) at different temperatures for 20 min

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Entry	Temp. (°C)	Yield (%)	Yield (%)[a]
			a **Pre-activated TiO$_2$ catalyst (450 °C, 1.5 h).**
1	60	0	25
2	80	0	81
3	100	99	97
4	120	72	70
5	160	37	38
6	200	31	30

Table 2 Benzoic acid (**1**)/benzylamine (**2**) amidation (TiO$_2$ 33.3 wt%, 100 °C) at different reaction times

Entry[a]	Time (min)	Yield (%)
	a TiO$_2$ catalyst without any pre-activation. *b* Reaction performed in a multimode MW reactor in organic solvents (toluene and acetonitrile). *c* Two-step reaction: 1st (benzoic acid + TiO$_2$); 2nd (amine addition). *d* Reaction performed without a catalyst.	
1	5	31
2	10	94
3	15	76
4	20	99 (<5)[b]
5	40	100 (<10)[b]
6	(20 + 20)[c]	77 (<5)[b]
7	(20 + 40)[c]	69 (<5)[b]
8	40	0 (0)[b]
9	40	0 (0)[b]
10	40	0[d]

The sequential addition of carboxylic acid and amine to the catalyst powder with two heating steps was deleterious (Table 2, entries 6 and 7).

The catalyst amount was varied over a range of 1.5–150 wt% of total reactant mass. Fig. 1 indicates that the reaction yield is directly proportional to the amount of the catalyst up to a value of 33 wt%, where the proportionality is reversed. The mole ratio of acid to amine was 1 : 1.1 under the same set of reaction conditions and no significant increase in yield was observed upon increasing the amine excess to over 5%.
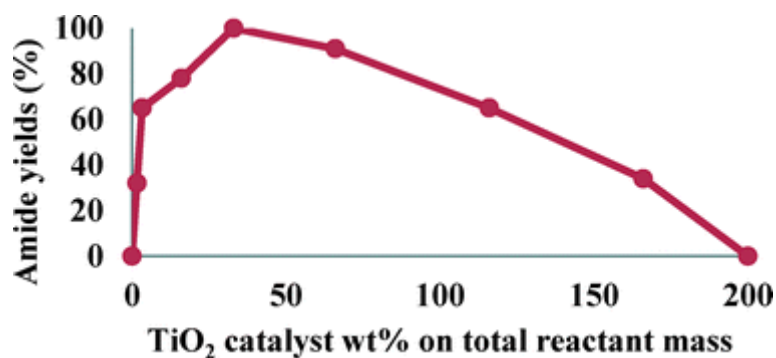
Fig. 1 Optimal catalyst loading without pre-activation (neat, 100 °C, 20 min).

3.1 Recyclability of TiO$_2$ catalyst

Catalyst recycling was investigated in the solvent-free amidation of benzoic acid (**1**) with benzylamine (**2**) (20 min, 100 °C, MW). Over 90% of the catalyst was easily recovered from the reaction mixture after each cycle in a process that included washing with ethyl acetate, centrifugation and drying under vacuum. TiO$_2$ was regenerated *via* heating in a muffle furnace for 1.5 h at 450 °C. The reused catalyst afforded the amide without any appreciable loss in efficiency for up to five runs (99, 95, 93, 92 and 90%, respectively, Table 3).

Table 3 TiO$_2$ recycling: MW monomode amidation (100 °C, 20 min) between benzoic acid and benzylamine

| Entry[a]	Cycle[b]	Yield (%)
		a TiO$_2$ catalyst 33 wt%. *b* TiO$_2$ catalyst regenerated *via* heating in a muffle furnace (450 °C; 1.5 h). *c* TiO$_2$ catalyst used directly without any pre-activation.
1	0[c]	99
2	1	95
3	2	93

Entry[a]	Cycle[b]	Yield (%)
4	3	92
5	4	90
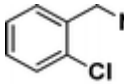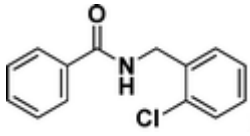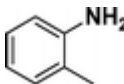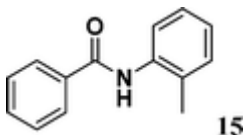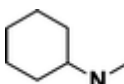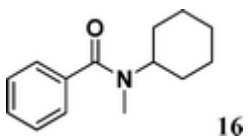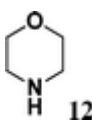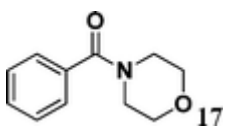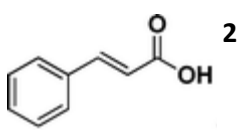
All the substrates used and the results achieved in the present investigation are summarized in Table 4. The benzylamine that was *ortho*-substituted with an electron-withdrawing group (chloro) also gave high amide yield (77%) upon reacting with benzoic acid (entry 3c). Although a little slower than primary amines, even the more sterically hindered 1-phenylethanamine furnished the amide with benzoic acid in g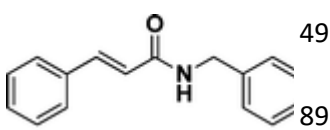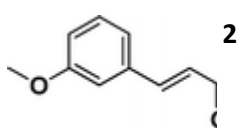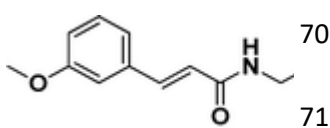ood yield (78%) (entry 2c), while *N*-methylcyclohexanamine and morpholine (entries 5c–6c) were less reactive (67% and 35%, respectively). It is interesting to note that *N*-benzilamide derivatives from different aromatic or aliphatic carboxylic acids can be obtained in good yields with the same protocol (entries 7–10).

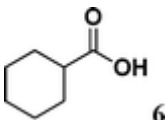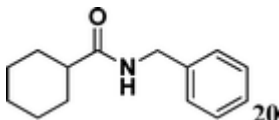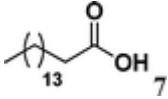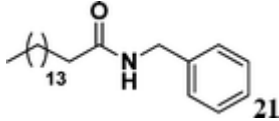**Table 4** Amidation reactions (100 °C) in the presence of TiO$_2$ (33.3 wt%) at different reaction times
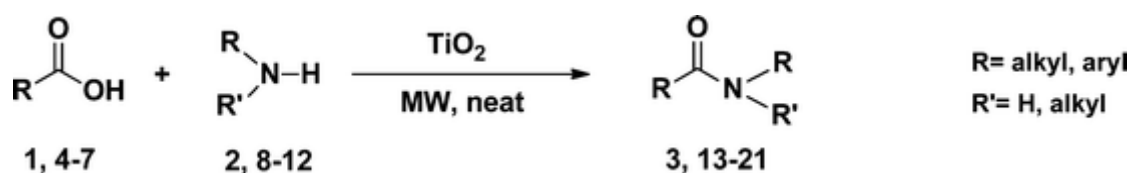
Entry	Carboxylic acid	Amine	Time (min)	Product	Yield (%)
			a 2-Step reaction: 1st (benzoic acid + TiO$_2$); 2nd (amine addition).		
1	a **1**	**2**	20	**3**	99
	b		40		100
2	a **1**		20		36
	b		40	**13**	71

Entry		Substrate	Temp	Product	Yield
	c		60		78
3	a **1**	2-chlorobenzylamine	20	**14**	20
	b		40		23
	c		60		77
4	a **1**	2-methylaniline	20	**15**	<1
	b		40		49
	c		60		55
5	a **1**	N-methylcyclohexylamine	20	**16**	17
	b		40		54
	c		60		67
6	a **1**	morpholine **12**	20	**17**	14
	b		40		20
	c		60		35
7	a	cinnamic acid **2**	20		49
	b		40		89
	c		60		98
8	a	**2**	20		70
	b		40		71
	c		60		96 (24)[a]
9	a		**2**	20		90

	b	6	40	20	93 (77)[a]
	c		60		95
10	a	7	2 20	21	62
	b		40		89
	c		60		92

3.2 IR spectroscopy of adsorbed benzoic acid

For the sake of operational condition simplicity, the catalyst was used as received or after calcination in a muffle furnace and subsequent re-exposure to ambient air at room temperature, resulting in the extensive rehydration of the TiO_2 particle surface. Hence, in both cases the catalyst was used in a surface hydrated form. Previous studies on the dehydration of this material indicated that a significant number of H_2O molecules remain adsorbed onto the surface after outgassing at 100 °C (*i.e.*, the optimized reaction temperature in the present study), under high vacuum,[32] which are more severe conditions than in the reactor. On such a basis, an investigation into the adsorption of benzoic acid (giving origin to the highest yield obtained) onto the hydrated catalyst was carried out by *in situ* IR spectroscopy (Fig. 2). Because of the presence of surface hydroxy groups, contributing to the high-frequency region of the IR spectrum of TiO_2 together with the stretching modes of adsorbed water molecules, the effect of the absorption of benzoic acid onto the latter must be monitored through the evolution of the band of the δH_2O deformation mode (signal at 1621 cm^{-1}, curve a). However, the overlapping between this band and part of the spectral pattern of benzoic acid required the substitution of H_2O molecules with D_2O ones, which gave the δD_2O band at 1200 cm^{-1} (curve b). To avoid possible D/H isotopic exchange, deuterated benzoic acid molecules, H_5C_6COOD molecules, hereafter BA-d, were used for this experiment.
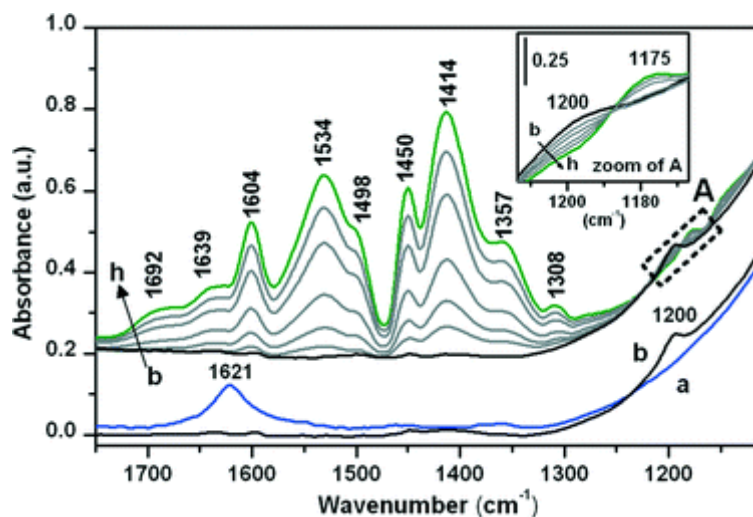
Fig. 2 IR spectra of: (curve a) TiO₂ activated at 450 °C, then contacted with water vapor pressure and subsequently outgassed at b.t. for 30 min; (curve b) after D₂O adsorption/desorption cycles (until attainment of spectra invariance) and subsequent outgassing at b.t. for 30 min; (curves c–h) increasing amounts of BA-d adsorbed from the vapor phase. Inset: zoomed view of the 1215–1165 cm⁻¹ range of the spectra from D₂O irreversibly adsorbed at b.t. (curve b) to its complete displacement by BA-d (curve h). The full range spectra are reported in Fig. S1 in the ESI.†

Therefore, BA-d vapors, produced by the sublimation of BA-d crystals contained in a reservoir connected to the IR cell, were dosed onto the D₂O molecule hydrated catalyst.

The progressive adsorption of BA-d resulted in the appearance of several components in the 1700–1100 cm⁻¹ range (curves c–h). Besides the signals of C=C and C–H modes of the aromatic ring at 1639, 1604, 1498, 1450, 1357, and 1175 cm⁻¹, bands at 1534 and 1414 cm⁻¹ from the COO⁻ antisymmetric and symmetric stretching modes, respectively, of adsorbed benzoate species and components at 1692 and 1308 cm⁻¹ assigned to the νC=O and δCOD modes, respectively, of –COOD moieties were observed.[33–36]

Focusing on the low-frequency part of the spectra, it can be seen that the δD₂O band at 1200 cm⁻¹ progressively decreases in intensity as the amount of adsorbed BA-d increases and this clearly indicated the displacement of adsorbed D₂O molecules by benzoic acid. This finding indicates that carboxylic acid molecules experience direct interaction with the TiO₂ surface, even when the surface is hydrated, where they can then undergo catalytic activation towards amidation.

It seems reasonable that the activation of the benzoate species carboxylate groups should occur as proposed for formate and acetate species adsorbed on TiO₂, *i.e.* a withdrawal of the electron density from

the C atom of the carboxylate moiety resulting from the interaction of the oxygen atoms of such group with surface Ti^{4+} ions, acting as Lewis acid centres.[28] The investigation of the possible activation of benzoic acid molecules adsorbed in a non-deprotonated form will represent a future extension of this study.

Conclusions

Herein we have described a novel, efficient solvent-free protocol for the amidation reaction using non-toxic and inexpensive TiO_2 powder. The advantages of this environmentally benign and safe protocol include a simple reaction setup, very mild reaction conditions and high product yields (significantly more convenient than non-catalysed processes),[27] short reaction times and catalyst recycling.

Acknowledgements

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