



# Use of immobilized organic base catalysts for continuous-flow fine chemical synthesis

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## ARTICLE INFO

### Article history:

Received 21 May 2008

Revised 9 July 2008

Accepted 10 July 2008

### Keywords:

Nitroaldol condensation

Michael addition

Heterogeneous catalysis

Organic–inorganic hybrid composites

Supported catalysts

Continuous-flow processes

## ABSTRACT

A continuous-flow two-step process for the production of multifunctional intermediate compounds was performed with a combination of two column reactors packed with different organic immobilized catalysts. The first step of the reaction, nitroaldol condensation between aromatic aldehydes and nitromethane, is promoted by a silica gel-supported primary amine; the second step, Michael addition of  $\beta$ -dicarbonyl compounds to the nitrostyrenes obtained in the first step, is catalyzed by a silica gel-supported guanidine TBD. In both cases, the catalysts can be directly reused for several runs with no significant changes in activity.

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## 1. Introduction

Numerous products for fine, pharmaceutical, and material chemistry with an ever-increasing level of complexity have been developed over the past several decades through multistep synthetic methods. In multistep synthesis, the preparative difficulties increase significantly with the number of steps, due mainly to extensive isolation and purification operations. These drawbacks can be overcome by exploiting a multistep-sequential synthetic methodology, namely by adding reagents and/or catalysts in a sequential manner without isolating the previously formed intermediates [1]. Moreover, in many cases, multicomponent reactions can be used to assemble three or more starting compounds into the final target molecule in a single reaction vessel.

The successful outcome of a given multistep sequential or multicomponent process depends on a fine balance of equilibria and a convenient sequence of reversible and irreversible steps [2]. In principle, complex organic compounds also can be prepared using a combination of column reactors with supported catalysts and/or reagents [3]. This approach uses columns packed with immobilized organic or inorganic catalysts/reagents. Starting materials are added to the top of the column and by means of gravity or pressure passed through the packing, where they react, giving the product recovered at the bottom of the setup [4].

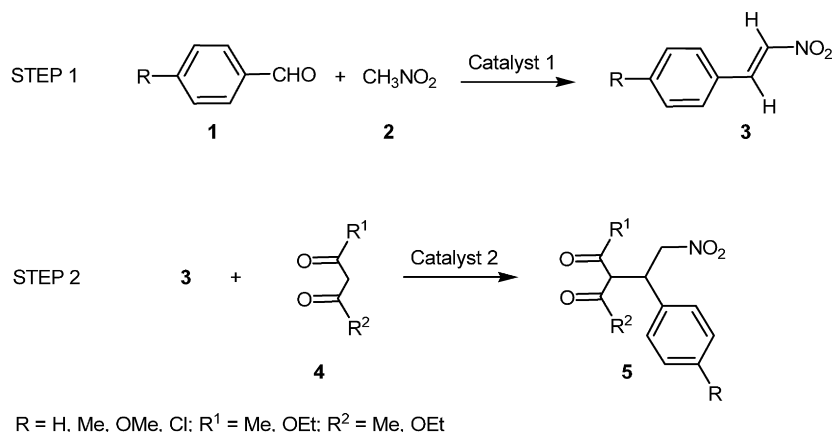
The use of catalysts immobilized onto solid supports for the liquid-phase fine chemical synthesis allows their easy separation from the reaction mixture and reuse for many runs, finally achieving great advantages, such as saving energy, minimizing waste production, and delivering products of higher purity [5]. Moreover, supported catalysts can be applied in packed-bed or monolithic reactors for continuous-flow processes [6,7].

These relatively new technologies offer many fundamental and practical advantages of relevance to the pharmaceutical and fine chemical industries, including facile automation, reproducibility, safety, and process reliability [7–9]. The improved performance of these catalytic reactors is attributed to faster heat transfer and mixing as a result of the increased surface area-to-volume ratio [10]. But despite the growing number of studies on this topic, only a few reports to date have discussed the use of catalytic packed-bed (micro) reactors applied to continuous-flow synthetic chemistry [11,12].

As a result of a more general project aimed at achieving basic information to design micro and monolithic reactors for organic syntheses, we have recently patented the continuous-flow synthesis of enantiomerically enriched (*R,R*)-chrysanthemoid acid through a tubular reactor packed with silica-supported chiral copper(II)-BOX catalyst [13]. Here we present the results of our studies on the setup of two catalytic reactors able to produce nitroaldol condensation and the Michael reaction under continuous-flow conditions (Scheme 1) [14]. The combination of both processes allows the production of multifunctional compounds **5**, which are valuable

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**Scheme 1.** Multistep synthesis of products **5**.

intermediates in fine and pharmaceutical chemistry, because nitrocompounds can be transformed into amines, ketones, carboxylic acids, and other important components [15,16].

According to Scheme 1, the multifunctional compounds **5** can be produced by nitroaldol condensation directly between aromatic aldehydes **1** and nitromethane **2**, giving nitrostyrenes **3** (step 1), followed by Michael addition of  $\beta$ -dicarbonyl compounds **4** to the electron-poor carbon–carbon double bond of compounds **3** (step 2) [17,18].

## 2. Experimental

### 2.1. Materials

All chemicals and solvents were used as received except benzaldehyde, which was distilled before use. Thin-layer chromatography (TLC) was performed with Merck 60 F<sub>254</sub> silica gel plates, and compounds were visualized with UV light.

Starting materials for catalyst preparation were as follows: silica gel KG-60 (size 0.040–0.080 mm; surface area 480–540 m<sup>2</sup>/g; pore volume 0.74–0.84 cm<sup>3</sup>/g), (3-aminopropyl)triethoxysilane (99%, Aldrich), (3-diethylaminopropyl)trimethoxysilane ( $\geq 90\%$ , Fluka), (3-methylaminopropyl)trimethoxysilane ( $\geq 97\%$ , Fluka), 3-(2-aminomethylaminopropyl)trimethoxysilane ( $>98\%$ , Fluka), (3-glycidyloxypropyl)trimethoxysilane ( $>97\%$ , Fluka), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (98%, Aldrich), and 1,1,1,3,3,3-hexamethyldisilazane (99.9%, Aldrich).

Starting materials for synthetic studies were as follows: benzaldehyde ( $\geq 99\%$ , Fluka), 4-methylbenzaldehyde ( $\geq 96\%$ , Fluka), 4-chlorobenzaldehyde ( $\geq 97\%$ , Aldrich), 4-methoxybenzaldehyde (98%, Aldrich), ethyl acetoacetate ( $\geq 99\%$ , Riedel-de-Haën), 2,4-pentanedione ( $\geq 99\%$ , Aldrich), diethylmalonate (99%, Aldrich), and nitromethane (96%, Aldrich).

### 2.2. Catalyst preparation

Silica-supported organic catalysts can be prepared by a sol–gel or postmodification method. We used the postmodification approach for the preparation of all silica-supported bases, because catalysts with lower base loads gave better yields in shorter reaction times [19]. The higher activity of the catalysts prepared by the postmodification method compared with those prepared by the sol–gel method likely is due to the larger surface area ( $\sim 250$  m<sup>2</sup>/g for the postmodification method vs.  $\sim 135$  m<sup>2</sup>/g for the sol–gel method [20]).

#### 2.2.1. Preparation of KG-60-supported amines

Catalysts were prepared according to the methods reported in the literature by grafting the organic groups to the surface silanols

of the KG-60 silica, previously dried at 350 °C overnight, using trialkoxyorganosilanes. In particular, 3-aminopropyltriethoxysilane, *N*-methyl-3-aminopropyltrimethoxysilane, *N,N*-diethyl-3-aminopropyltrimethoxysilane, and 3-(2-aminoethylamino)propyltrimethoxysilane gave solid basic catalysts, referred to as KG-60-NH<sub>2</sub> [21], KG-60-NHMe [22], KG-60-NEt<sub>2</sub> [23], and KG-60-NH(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub> [24], respectively.

A typical preparation was as follows. Dried silica (10 g) was added to toluene (150 ml), followed by the selected trialkoxysilane (30 mmol). The mixture was refluxed for 18 h under mechanical stirring. The resulting slurry was cooled to room temperature and the modified silica was filtered, washed with toluene (50 ml), acetone (50 ml), water (50 ml), and finally acetone (2  $\times$  50 ml). After being allowed to dry at room temperature under vacuum, the modified silica was dried in an oven at 100 °C for 10 h.

#### 2.2.2. Preparation of silica-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)

The supported catalyst was prepared by modifying the method of Jacobs et al. [25] in two steps. First, (3-glycidyloxypropyl)trimethoxysilane (10 ml, 46.5 mmol) was added dropwise under nitrogen to a solution of TBD (6.5 g, 46.9 mmol) in dry DMF (65 ml). The resulting mixture was stirred for 24 h at room temperature. Second, a suspension of KG-60 silica (20.1 g previously sieved and dried) in dry toluene (150 ml) was refluxed for 1 h under nitrogen, after which the solution obtained in the first step was added and refluxed for additional 16 h under nitrogen. The modified silica thus obtained was filtered and washed with toluene (120 ml), dichloromethane (200 ml), and methanol (100 ml), then extracted with a diethyl ether dichloromethane mixture (150/150 ml) in a Soxhlet apparatus overnight. Finally, the modified silica was dried.

#### 2.2.3. Preparation of the capped KG-60-TBD-SiMe<sub>3</sub> [26]

Dried silica gel KG-60 (8 g), previously heated at 350 °C for 3 h and dried by vacuum at room temperature for 2 h, was introduced into a flask containing dry toluene (120 ml). Then (3-glycidyloxypropyl)trimethoxysilane (4.0 ml, 17 mmol) was added, and the mixture was heated at reflux under stirring for 18 h. The modified silica was filtered and washed with dichloromethane (20 ml). The powder was then mixed with HMDS (19.4 g, 120 mmol), and the mixture was heated at 60 °C under stirring for 2 h. The powder was filtered and washed with dichloromethane (20 ml), then introduced into a flask containing a solution of TBD (2.45 g, 17.58 mmol) in dry toluene (120 ml), with the resulting mixture stirred at room temperature for 10 h. The catalyst was filtered, washed with dichloromethane (20 ml), and extracted with a Soxhlet apparatus for 10 h using a 1:1 dichloromethane/diethyl ether

solution (200 ml). Finally, the catalyst was filtered and dried under vacuum at room temperature.

### 2.3. Catalyst characterisation

All materials were characterised with respect to their compositional, textural, and surface properties. The loadings of the organic groups were calculated from the nitrogen content by elemental analysis performed with a Carlo Erba CHNS-0 EA1108 elemental analyzer.

Thermogravimetric analyses, performed with a Setaram TG-DTA 92 thermobalance in He/O<sub>2</sub> flow, revealed that all of these materials were thermally stable and thus did not release organic fragments until 300 °C. The N<sub>2</sub> adsorption–desorption isotherms, carried out at –196 °C on a Micromeritics ASAP 2010, were used to determine the specific surface areas, S<sub>BET</sub>. Before each measurement, the samples were outgassed at 110 °C and 1.33 × 10<sup>–4</sup> Pa for 12 h.

### 2.4. Reaction procedures

#### 2.4.1. Nitroaldol condensation under batch conditions

To a solution of the selected benzaldehyde (2.46 mmol) in dry nitromethane (3 ml), the catalyst (3% mmol of supported amine with respect to aldehyde) was added. The mixture was heated at 75 °C and stirred for 1 h. The crude was then filtered and the catalyst recovered after washing with ethyl acetate (20 ml). Finally, yield, conversion and selectivity were determined by gas chromatography (GC) through internal standard analysis.

#### 2.4.2. Nitroaldol condensation under continuous-flow conditions

KG-60 silica (0.77 or 0.65 g depending on KG-60-NH<sub>2</sub> amount), previously sieved to 80 mesh and dried at 350 °C for 3 h, was mixed with the KG-60-NH<sub>2</sub> catalyst (0.23 g, 0.25 mmol or 0.35 g, 0.37 mmol; 3.0% and 4.5% mol with respect to benzaldehyde). The powder was packed in the reactor, an oil-jacketed steel HPLC column (6.0 cm length × 0.8 cm inner diameter), along with nitromethane (10 ml). The jacketed column was heated to the selected temperature, and a solution of the aromatic aldehyde (8.20 mmol) in dry nitromethane (4.2 ml) was passed under pressure at a selected flow rate using a syringe pump. The crude was collected at the bottom of the column after rinsing with ethyl acetate (20 ml).

#### 2.4.3. Michael addition of β-dicarbonyl compounds to nitrostyrene under batch conditions

To a solution of nitrostyrene (0.30 g, 2.0 mmol) in the selected solvent (1.5 ml), β-dicarbonyl compound (2.0 mmol) and the catalyst (10% mmol) were added. The mixture was stirred at room temperature under nitrogen for 4 h. The catalyst was filtered and washed with ethyl acetate (15 ml), after which the crude was collected.

#### 2.4.4. Michael addition of β-dicarbonyl compounds to nitrostyrene under continuous-flow conditions

KG-60-TBD-SiMe<sub>3</sub> catalyst sieved at 80 mesh (1.00 g, 0.73 mmol) was packed in an oil-jacketed steel HPLC column (similar to that used for the nitroaldol condensation) with THF (10 ml). Then a solution of the β-dicarbonyl compound (22.0 mmol) and nitrostyrene (1.08 g, 7.3 mmol) in THF (14 ml) was passed through under low pressure by a syringe pump (~0.2 bar) at room temperature for 1 h. The crude was collected at the bottom of the column.

#### 2.4.5. Continuous-flow two-step catalytic synthesis of 3-carbethoxy-4-phenyl-5-nitro-2-pentanone (5b)

An oil-jacketed steel HPLC column (6.0 cm long × 0.8 cm i.d.) was packed with KG-60-NH<sub>2</sub> catalyst (0.35 g, 0.37 mmol) of the

supported amine; 4.5% mol) mixed with KG-60 silica sieved at 80 mesh and previously heated at 350 °C for 3 h (0.65 g), with nitromethane (10 ml). The column was heated to 110 °C, after which a solution of distilled benzaldehyde (0.87 g, 8.20 mmol) in dry nitromethane (4.2 ml) was added. The solution was passed through a syringe pump at 0.5 bar pressure with a 0.25 ml/min flow rate. The crude was recovered after the column was rinsed with dichloromethane (30 ml) at 35 °C. Nitrostyrene **3a** was produced in a 97% yield (GC analysis). All solvents were distilled off, and the resulting yellow oil was diluted with a solution of ethyl acetoacetate (3.1 g, 24.0 mmol) in THF (15 ml). This solution was passed through a second column, similar to that used previously, packed with KG-60-TBD-SiMe<sub>3</sub> (1.08 g, 0.79 mmol) in THF (15 ml) for 1 h at room temperature under 0.2 bar pressure. The crude was recovered, and the column was rinsed with ethyl acetate (20 ml). Product **5b** was obtained in an 85% overall yield. Products **3a–d** and **5a–c** gave melting points and spectral data consistent with values reported previously [22,27,28].

## 3. Results and discussion

Amines supported on silica and organic polymers have been used occasionally to promote nitroaldol and Michael reactions under batch conditions [19,23,29,30]. However, the problem of performing the reactions under continuous-flow conditions remains to be addressed. To effectively compare the catalytic activity of supported basic organic catalysts in both reactions with that observed in previous studies, we carried out a comparison using an uniform series of solid catalysts prepared by anchoring different organic bases to the same support, namely amorphous silica KG-60, through the same postsynthetic method. In contrast, in the previous studies on this topic, reactions were carried out with catalysts supported on different materials (e.g., amorphous silica, micelle-templated silica, mesoporous MCM-41 silica, polystyrene) and/or prepared with different methods (e.g., postsynthesis, sol-gel, copolymerization), yielding results that are not directly comparable.

A nonswelling material such as amorphous silica KG-60, sieved at 80 mesh, was used as the support, because a major issue encountered in packing channels with supported catalysts is the pressure drop across the channel caused by either swelling or the size of the packing material [31,32]. In the nitroaldol condensation between benzaldehyde and nitromethane [20] (Scheme 1, step 1), primary, secondary, and tertiary amines, as well as TBD, were used as catalysts supported on amorphous silica KG-60 through a convenient spacer.

Batch reactions were carried out by stirring freshly distilled benzaldehyde (2.46 mmol) in nitromethane (3 ml) used as a solvent-reagent for 1 h at 75 °C in the presence of 3% mol catalyst (with respect to benzaldehyde) under nitrogen, to avoid oxidation of the benzaldehyde to benzoic acid, which could react with the supported amine giving the amide and definitively poison the catalyst [33]. The reaction directly gave (*E*)-nitrostyrene **3a** as the sole isomer, accompanied by polynitroderivative byproducts due to the polymerization of **3a** and/or addition of a second molecule of nitromethane to **3a**.

The results reported in Table 1 confirm that the yield and selectivity of product **3a** were affected mainly by the nature of the supported amine rather than by the physicochemical parameters of the catalysts, such as surface area or basic strength. Indeed, different supported amine catalysts with comparable surface areas and similar amine loadings gave product **3a** with completely different yield and selectivity (Table 1, entries 2 and 4). Moreover, the supported propylamine gave product **3a** with yield and selectivity greater than that of the more basic supported TBD (propylamine

**Table 1**  
Catalytic efficiency of organic bases supported on amorphous silica KG-60 in the batch nitroaldol condensation between benzaldehyde and nitromethane as solvent-reagent

Entry	Catalyst	Loading (mmol/g)	$r_0 \cdot 10^4$ (mol/(min g)) <sup>a</sup>	Surface area (m <sup>2</sup> /g)	<b>1a</b> conv. (%)	<b>3a</b> yield (Sel. <sup>b</sup> ) (%)
1	KG-60-NH <sub>2</sub>	0.65	4.24	254	76	75 (99)
2	KG-60-NH <sub>2</sub>	1.06	6.55	254	100	98 (98)
3	KG-60-NH(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	1.24		225	52	36 (70)
4	KG-60-NHMe	0.88		245	75	28 (37)
5	KG-60-NEt <sub>2</sub>	1.12		210	28	4 (15)
6	KG-60-TBD	0.67		260	67	26 (38)

<sup>a</sup> Initial rate of formation of **3a** per gram of catalyst.

<sup>b</sup> (Yield/Conversion) × 100.

**Table 2**  
Catalytic efficiency of organic bases supported on amorphous silica KG-60 in the batch Michael addition of acetylacetone to nitrostyrene

Entry	Catalyst	Solvent ( $E_T^N$ ) <sup>a</sup>	Loading (mmol/g)	<b>3a</b> conv. <sup>b</sup> (%)	<b>5a</b> yield (Sel. <sup>c</sup> ) (%)
1	KG-60-NHMe	THF (0.207)	0.88	92	76 (82)
2	KG-60-NEt <sub>2</sub>	THF (0.207)	1.12	81	43 (53)
3	KG-60-TBD	THF (0.207)	0.67	80	69 (86)
4	KG-60-TBD	CH <sub>2</sub> Cl <sub>2</sub> (0.309)	0.67	86	78 (90)
5	KG-60-TBD	EtOH (0.654)	0.67	92	67 (73)
6	KG-60-TBD	Toluene (0.099)	0.67	63	40 (63)
7	KG-60-TBD	Acetylacetone (0.571)	0.67	100	99 (99)
8	KG-60-TBD-SiMe <sub>3</sub> <sup>d</sup>	THF (0.207)	0.73	89	87 (98) <sup>e</sup>

<sup>a</sup> Normalised  $E_T(30)$  parameter (Reichardt) [37].

<sup>b</sup> Relative to the conversion of nitrostyrene.

<sup>c</sup> (Yield/Conversion) × 100.

<sup>d</sup> Surface area: 265 m<sup>2</sup>/g.

<sup>e</sup> Acetylacetone/nitrostyrene 3:1 molar ratio.

$pK_b = 3.4$ , **3a** yield = 98%, **3a** selectivity = 98%; TBD  $pK_b = -11.0$ , **3a** yield = 26%, **3a** selectivity = 38% (Table 1, entries 2 and 6).

This behaviour has been attributed to the fast initial production of a supported reactive imine intermediate through reaction of the supported propylamine with benzaldehyde, as can be easily verified by FT-IR spectra [19]. Product **3a** arose from the nitro-Mannich addition of nitromethane (activated as nitronate anion) to the supported imine, followed by the  $\beta$ -scission [34]. As expected, when the reaction was carried out in the presence of KG-60-NH<sub>2</sub> samples containing different amounts of anchored propylamine, the initial reaction rate [35] was proportional to the amount of the supported amine, indicating that the reaction should be of first order with respect to the catalyst concentration (Table 1, entries 1 and 2).

We also analyzed the progress of benzaldehyde **1a** conversion versus time in the model reaction performed in the presence of KG-60-NH<sub>2</sub> catalysts. The conversion reached 100% after 60 min; the data are better described by a first-order irreversible kinetic with  $k = 1.2 \times 10^{-2}$  ( $1.9 \times 10^{-3}$ ) min<sup>-1</sup>.

Concerning the effect of the supported base, it is well recognised that different basic catalysts, such as KG-60-NHMe, KG-60-NEt<sub>2</sub> and KG-60-TBD, that exhibit basic sites with medium to high basic strength can promote the reaction through a typical nitroaldol mechanism involving addition of the nitronate anion to the aldehyde [17]. The significant difference between the two chemical pathways (i.e., the nitro Mannich and nitroaldol mechanisms) is the main factor accounting for the different catalytic activities.

The optimization of step 2 under batch conditions was successively studied. Reactions were performed at room temperature using nitrostyrene (2 mmol) and acetylacetone (2 mmol) as model reagents in the presence of the supported catalysts used in the previous step (10% molar ratio) in different solvents [36] (Table 2). Table 2 reports only the results obtained with secondary and tertiary amines as well as TBD, because the primary amine gave extremely poor yield and selectivity. In this case, the basic strength of the supported catalyst plays an important role, and the catalytic

efficiency (namely yield and selectivity in product **5a**) depends on the  $pK_b$  value.

Concerning aliphatic amines, the secondary amine ( $pK_b \approx 3.2$ ) afforded product **5a** in a 76% yield, whereas the less basic tertiary amine ( $pK_b \approx 3.4$ ) gave product **5a** in a lower yield (43%) (Table 2, entries 1 and 2).

The mostly higher yields and selectivities observed with TBD-supported catalysts can be attributed mainly to their higher basicity, resulting in a greater concentration of the active acetylacetone carbanion [38]. This increases the Michael addition rate and shortens the permanence time of the very reactive nitrostyrene in contact with the siliceous material, thereby minimising byproduct formation (Table 2, entries 2 and 3).

However, the activity of KG-60-TBD catalyst was strongly affected by the polarity of the solvent, because the reaction involves charged species in the transition state (Table 2, entries 3, 4, and 6). In particular, it was found that the higher the polarity of the solvent, the greater the nitrostyrene conversion and product yield.

The maximum catalytic efficiency was observed when acetylacetone was utilised as solvent-reagent, because under these conditions, the concentration of the acetylacetone anion likely reached the maximum value (Table 2, entry 7).

A seemingly anomalous behaviour was observed when the reaction was carried out in ethanol (Table 2, entry 5): High nitrostyrene conversion (92%) was accompanied by a surprisingly low **5a** yield value (67%). This result can be rationalised by taking into account that ethanol is a protic solvent able to catalyse the nitrostyrene polymerisation, which also can be promoted by silica surface free silanols [39]. Interesting results were achieved by preventing the negative effect of the surface silanols through silanization with hexamethyldisilazane (HMDS) using KG-60-TBD-SiMe<sub>3</sub> as catalyst with a molar ratio acetylacetone/nitrostyrene = 3:1 (Table 2, entry 8) [40].

For both reactions (nitroaldol condensation and Michael addition), we performed the Sheldon test [41] to confirm the inactivity of the filtered reaction mixture and the reusability of the catalyst in both cases.

In light of the foregoing results, we planned to perform both reactions under continuous-flow conditions using the best catalysts identified in the batch experiments. First, nitroaldol condensation (Scheme 1, step 1) was studied using a tubular reactor. The reactor was prepared with an oil-jacketed steel HPLC column (6.0 cm long × 0.8 cm i.d.) packed with 0.23 g of KG-60-NH<sub>2</sub> “diluted” into 0.77 g of KG-60 silica heated previously to 350 °C for 3 h. Both siliceous materials were sieved at 80 mesh before use. The column reactor was washed with nitromethane and used immediately, taking into account the optimum conditions found in the previous batch experiments. A solution of benzaldehyde (0.87 g, 8.2 mmol) in nitromethane (4.2 ml) was passed through the column at different flow rates and temperatures by a syringe pump. Low pressure (~0.2 bar) was applied at the top of the column to keep the flow constant during the entire residence time. The results are reported in Table 3.

**Table 3**

Continuous-flow nitroaldol condensation of benzaldehyde and nitromethane (solvent-reagent) over KG-60-NH<sub>2</sub> catalyst (1.06 mmol/g propylamine loading)

Entry	Catalyst/1 molar ratio	Residence time (min)	Flow rate (ml/min)	Temp. (°C)	1a conv. (%)	3a yield (Sel. <sup>a</sup> ) (%)
1	3/100	25	0.12	56	40	33 (82)
2	3/100	35	0.08	56	60	45 (75)
3	3/100	50	0.06	56	65	50 (77)
4	3/100	35	0.08	75	76	61 (80)
5	4.5/100	12	0.25	110	98	95 (97)

<sup>a</sup> (Yield/Conversion) × 100.

Benzaldehyde **1a** conversion and nitrostyrene **3a** yield were evaluated from the entire reaction mixture recovered at the end of the flow-through process. By using 3% mol of KG-60-NH<sub>2</sub> with respect to benzaldehyde passed, the conversion of **1a** and the yield of **3a** increased with increasing residence time from 25 to 50 min, reaching modest values in all cases (40%–65% **1a** conversion; 75%–82% **3a** selectivity) (Table 3, entries 1–3).

Ideally, the flow rate should be slow enough to guarantee full conversion of the starting materials and to give only the desired product at the end of the reaction. However, by directly applying the best reaction parameters achieved with batch experiments to the column reactor, the selectivity toward nitrostyrene **3a** dropped down mainly due to the production of 1,3-dinitro-2-phenylpropane by the further addition of nitromethane to nitrostyrene. To overcome this drawback, the residence time was shortened to 12 min, the reaction temperature was increased to 110 °C, and the amount of catalyst was increased to 4.5%. Under these conditions, a low pressure of ~0.5 bar was applied to ensure a regular flow inside the column. The efficiency of the column reactor was enhanced significantly, and product **3a** was obtained with 95% yield and 97% selectivity without the need to isolate the intermediate nitroalcohol (Table 3, entry 5) [42].

The catalytic reactor could be reused efficiently after simple rinsing with nitromethane. A second reaction mixture was then passed through the reactor under the same conditions, giving product **3a** in a 93% yield and 96% selectivity.

The continuous-flow condensation process was extended to some aromatic aldehydes under the optimized conditions of 12 min residence time and 110 °C, giving the small series of substituted nitrostyrenes reported in Table 4 with interesting yields and selectivities.

Table 4 shows that the introduction of an electron-withdrawing substituent at the *para* position of the aromatic aldehyde resulted in a lower yield of the corresponding nitrostyrene (entry 4). This phenomenon is in good agreement with the presence of supported imine intermediacy. Indeed, in an early comparative study, Santerre et al. [43] reported that the rate of imine formation from substituted aromatic aldehydes and aliphatic amines decreased significantly as the electron-withdrawing power of the substituent on the aromatic ring increased.

We next investigated the continuous-flow Michael addition of acetylacetone to nitrostyrene under the best conditions found in the batch experiments (Scheme 1, step 2). We performed reactions over the KG-60-TBD-SiMe<sub>3</sub> catalyst using THF as the solvent. Preparation of the packed column-reactor was similar to that described above, using a tube with the same dimensions packed with 1.0 g of KG-60-TBD-SiMe<sub>3</sub> (loading value, 0.73 mmol/g) sieved at 80 mesh. After the column-reactor was washed with THF, a solution of acetylacetone (2.2 g, 22.0 mmol) and nitrostyrene (1.08 g, 7.3 mmol) in THF (14 ml) was passed through with a syringe pump under low pressure (~0.2 bar) at room temperature (residence time, 35 min). Product **5a** was obtained in 90% yield (98% selectivity). The same column-reactor could be used, after accurate rinsing with ethyl acetate, to prepare some other Michael adducts between

**Table 4**

Preparation of substituted nitrostyrenes via continuous-flow nitroaldol condensation over KG-60-NH<sub>2</sub> catalyst (1.06 mmol/g propylamine loading)<sup>a</sup>

Entry	Product	3	Yield (Sel. <sup>b</sup> ) (%)
1		<b>3a</b>	95 (97)
2		<b>3b</b>	97 (98)
3		<b>3c</b>	95 (98)
4		<b>3d</b>	65 (93)

<sup>a</sup> Experimental conditions: all reactions were performed using 8.2 mmol of the selected benzaldehyde in 4.2 ml of nitromethane in the presence of 0.35 g of KG-60-NH<sub>2</sub> and 0.65 g of KG-60; residence time: 12 min, temperature: 110 °C.

<sup>b</sup> (Yield/Conversion) × 100.

**Table 5**

Preparation of some Michael adducts of nitrostyrene with  $\beta$ -dicarbonyl compounds via continuous-flow procedure<sup>a</sup>

Entry	Product	5	Yield (Sel. <sup>b</sup> ) (%)
1		<b>5a</b>	90 (98)
2		<b>5b<sup>c</sup></b>	92 (98)
3		<b>5c</b>	60 (72)

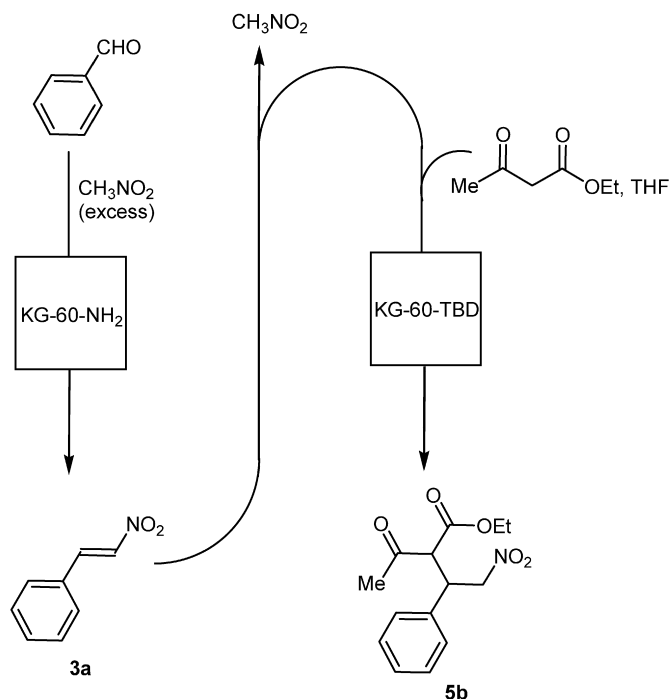
<sup>a</sup> Experimental conditions: all reactions were performed using 7.3 mmol of nitrostyrene, 22.0 mmol of the  $\beta$ -dicarbonyl compound in 14.0 ml of THF in the presence of 1.00 g of KG-60-TBD-SiMe<sub>3</sub>; residence time: 35 min, temperature: 25 °C.

<sup>b</sup> (Yield/Conversion) × 100.

<sup>c</sup> 48:52 diastereomeric mixture.

nitrostyrene and  $\beta$ -dicarbonyl compounds. Illustrative synthetic results are reported in Table 5. The lower reactivity observed with diethyl malonate (Table 5, entry 3) likely can be ascribed to the lower pK<sub>a</sub> value of the active methylene function [44].

Finally, the preparation of the multifunctional compound **5b** was studied by sequential two-step column catalytic methodology (Scheme 2). Benzaldehyde (0.9 g, 8.6 mmol) diluted in nitromethane (5 ml) was reacted through the KG-60-NH<sub>2</sub> column-reactor at 110 °C for 12 min of residence time under nitrogen, affording nitrostyrene **3a** in a 97% yield. The reaction mixture was then subjected to distillation to remove the excess of nitromethane



**Scheme 2.** Preparation of product **5b** via sequential column catalytic methodology.

(to avoid formation of byproducts derived from further addition of nitromethane to nitrostyrene). The resulting oil was diluted in THF (16 ml) containing ethyl acetoacetate (3.3 g, 25.2 mmol) and passed at room temperature through the second column-reactor filled with KG-60-TBD-SiMe<sub>3</sub>, washed previously with THF, with a residence time of 35 min. The final reaction mixture was collected, giving compound **5b** in an 85% overall yield with respect to benzaldehyde. Compounds like **5** represent useful precursors to various complex organic molecules of industrial interest [45] with functionalities that can be derived from both the nitro group and the  $\beta$ -dicarbonyl system [46].

#### 4. Conclusion

In this study, we have investigated the preparation of two packed-bed column reactors containing propylamine (KG-60-NH<sub>2</sub>) and guanidine TBD (KG-60-TBD-SiMe<sub>3</sub>) immobilized onto amorphous silica KG-60. The first catalyst, KG-60-NH<sub>2</sub>, was used to efficiently perform continuous-flow nitroaldol condensation between nitromethane and aromatic aldehydes, giving a small series of (*E*)-nitrostyrenes variously substituted on the aromatic ring (65%–97% yield, 93%–98% selectivity). The second catalyst, KG-60-TBD-SiMe<sub>3</sub>, gave a Michael addition of  $\beta$ -dicarbonyl compounds to nitrostyrenes affording polyfunctional compounds under continuous-flow conditions (60%–92% yield, 72%–98% selectivity).

The two-step reaction can be performed sequentially in a flow-trough mode, ensuring that any excess nitromethane is distilled off before  $\beta$ -dicarbonyl compound is added to the first reaction mixture. The catalytic reactors were reused for several runs, with no decrease in activity.

These products represent valuable intermediates being converted by classic methods into variously substituted  $\beta$ -amino ketones and  $\beta$ -amino acids, useful building blocks in pharmaceutical chemistry.

#### Acknowledgments

This research was partly supported by the MUR (National Project “Sintesi organiche ecosostenibili mediate da nuovi sistemi

catalitici”). The authors thank the Centro Interdipartimentale Misura (CIM), “G. Casnati,” for the NMR measurements.

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