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Synthesis of Nitro-Containing Compounds through Multistep Continuous Flow with Heterogeneous Catalysts

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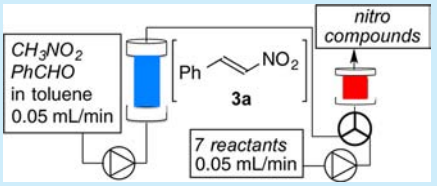
Supporting Information

ABSTRACT: Synthesis of β-nitrostyrene derivatives and their following reactions through two-step continuous-flow protocols with heterogeneous catalysts are described. In the first step to provide β-nitrostyrenes from aromatic aldehydes and nitromethane, readily available amino-functionalized silica gel was employed as a catalyst and gave the products continuously for at least 100 h with high selectivity. In the second step, reactions of β-nitrostyrenes, solid bases, immobilized bases, solid acids, and chiral supported metals and nonmetals were used as catalysts, and seven kinds of nitro-containing organic compounds could be effectively synthesized through the two-step continuous-flow systems.



Efficiency in synthesis is one of the most important factors in synthetic organic chemistry. Several transformation steps are required in the synthesis of complex target molecules; in general, intermediates are isolated and purified in each step. Avoiding a lengthy isolation process and purification of the intermediates would save time and resources while increasing chemical yields. One-pot synthesis is a strategy to improve the efficiency of chemical reactions whereby reactants are subjected to successive chemical reactions in just one reactor.[1] However, compatibility of substrates and reactants and formation and identification of impurities during the whole process are crucial, especially in pharmaceutical manufacturing. In addition, while the use of catalysts in organic synthesis is recommended from the viewpoint of green sustainable chemistry,[2] compatibility of catalysts and poisoning of catalysts are serious issues in one-pot synthesis.

Recently, organic synthesis using continuous-flow conditions has attracted much attention because of its environmental friendliness, efficiency, and safety.[3] Our group has focused on multistep continuous-flow synthesis with heterogeneous catalysts, which may not only enjoy advantages but also address disadvantages of one-pot synthesis.[4] We have recently demonstrated multistep continuous-flow synthesis of optically active (*R*)- and (*S*)-rolipram, an anti-inflammatory drug, by using four types of catalyst-embedded column modules.[5] In this work, appropriate use of four achiral/chiral heterogeneous catalysts converts five simple starting materials to the target chiral drug molecule accompanying eight transformations. While the efficiency of multistep continuous-flow synthesis has been demonstrated, applying flow organic reactions and heterogeneous catalysts to many target molecules is limited at this stage, and thus, development of protocols for multistep continuous-flow synthesis with heterogeneous catalysts is demanded. In this paper, we describe several two-step continuous-flow syntheses of nitro-containing compounds using heterogeneous catalysts.

Because of the strong electron-deficient property in their alkene part and ease of conversion of the nitro group to amino and other heterocycles, nitroalkenes are one of the most common and important intermediates in modern synthetic organic chemistry.[6,7] Among several methodological patterns to access this attractive intermediate, such as nitration of carbon−carbon double bonds and cross-coupling reactions, a two-step preparation through nitro aldol (Henry) reaction of aldehydes with nitroalkanes is the most common and versatile method applicable to diverse homologues. However, this method suffers from several disadvantages, such as harsh reaction conditions in the elimination process. To avoid this problem, a modified procedure via an aza-Henry reaction under primary (or secondary) amine catalysis has been developed by several groups.[8−14] In such modified processes, immobilized primary amines, (2-aminoethyl)aminopropyl or aminopropyl-functionalized mesoporous silica,[8,9] silica−alumina,[10] and clay[11,14] often play an important role in affording the desired nitroalkenes in high yields with high selectivities. Nevertheless, requirements of high reaction temperature and excess amounts of nitroalkanes and sometimes solvent amounts still remain to be overcome. In addition, to make the best use of such immobilized heterogeneous catalysts and to achieve greener, safer, more efficient, and continuous manufacture of such important organic intermediates, the use of continuous-flow reactors would be the ideal method.[15]

We began the present continuous-flow study on efficient and scalable production of β-nitrostyrene by examining effects of flow rate and concentration of substrates **1** and **2a** (Ar = Ph). A SUS column of 300 mm length and 10 mm diameter with

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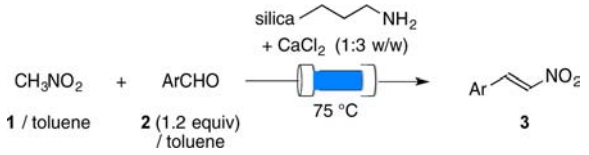
column ends was filled with a mixed catalyst system consisting of commercially available primary amine-functionalized silica gel (CHROMATOREX DM1020 NH) and anhydrous calcium chloride (Scheme 1). Toluene solutions of the substrate

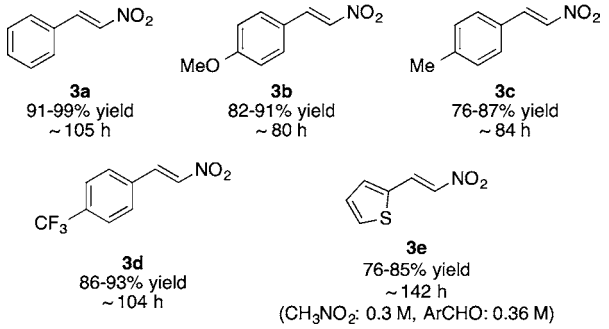
Scheme 1. Single-Step Synthesis of β-Nitrostyrenes



mixture (**1**:**2a** = 1:1.2) with various concentrations were fed by a plunger pump at the rate of 0.05−1.00 mL/min. For this first series of investigations, the total amount of nitromethane fed into the column was 40 mmol or more. In Figure S1 (see the Supporting Information), conversions of **2a** at the point of 36 mmol of **1** supplied to the catalyst column in eight experiments are plotted. It was shown that flow rate (<0.10 mL/min) and concentration (>0.2 M) were suitable for scalable production of the product (**3**).

We then examined the scope of aldehydes as well as scalability (Figure S2, see SI). Five kinds of aromatic and heteroaromatic aldehydes, **2a** (Ar = Ph), **2b** (Ar = 4-$MeOC_6H_4$), **2c** (Ar = 4-MeC_6H_4), **2d** (Ar = 4-$CF_3C_6H_4$), and **2e** (Ar = 2-thiophene), were successfully employed under the flow conditions of 0.5 M concentration and 0.05 mL/min flow rate, and the electronic nature of the aldehyde did not affect the reactivity. In all cases, the yields of **3** were kept at around 90% while more than 100 mmol of **1** and 120 mmol of **2** were supplied (Figure S2(a)), and the catalyst system was stable for more than 80 h (Figure S2(b)). In the case of thiophene-2-carboxaldehyde (**2e**), lower concentrations, 0.3 M for **1** and 0.36 M for **2e**, were required to secure a good yield (Scheme 2).

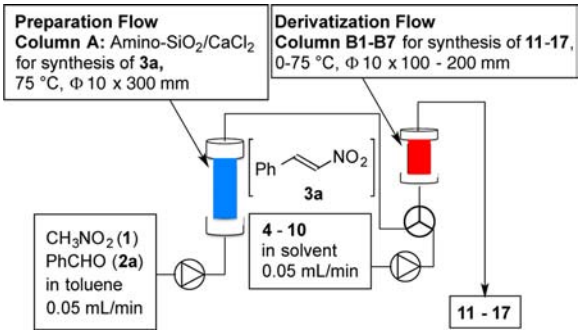
Scheme 2. Substrate Scope of β-Nitrostyrenes



We next connected the first column (synthesis of β-nitrostyrene derivatives **3**) with the second column, in which the reactions of **3** were carried out to afford other nitro-containing compounds under flow conditions (Scheme 3).[16] Although various types of reactions using β-nitrostyrene as a substrate are known, we here selected seven kinds of useful reactions: acid- or base-catalyzed conjugated addition,[17−19] asymmetric conjugated addition,[20,21] addition/cyclization,[22] and Morita−Baylis−Hillman-type reaction.[23]

The first flow was represented to be 0.20 M of **1** and a slight excess of **2a**, and the flow rate was set to be 0.05 mL/min. For the second flow, a new substrate was supplied at a suitable

Scheme 3. Two-Step Flow Reaction for Syntheses of Nitro-Containing Compounds



concentration of a toluene solution and was mixed with the first stream prior to the second column (column B). After stabilization (16 h), the supplement of the new substrate solution was started. All derivatization flows were catalytic processes, and thus, appropriate solid/heterogeneous catalysts were used as contents of column B. A SUS column of 100 mm length and 10 mm diameter with column ends was employed for each second step, and Celite or pure silica gel was appropriately packed with those catalyst materials. Five types of functionalization of the α-position of β-nitrostyrene by employing conjugate addition reactions conducted with different types of catalysts were examined. The addition reaction of primary amines such as benzylamine (**4**) successfully proceeded at room temperature using commercially available magnesium oxide as a solid base catalyst packed with Celite in column B1, and the corresponding product **11** was obtained in 87−95% yield during 50 h (Scheme 4).[17] The addition of ketoester **5** was performed using calcium oxide prepared from calcium hydroxide by calcination at 600 °C packed with Celite in column B2. The reaction in the second flow required gentle heating, while the product **12** bearing a quaternary carbon center was obtained in 82−98% yield during the same period.[18a] Solid acid-catalyzed conjugate addition was also possible using a metallosilicate-type solid acid such as aluminum-containing mesoporous silica MCM-41 packed in column B3. Indole **6** was employed successfully as a nucleophile for addition to nitrostyrene.[19] The corresponding product **13** was obtained in 81−92% yield at 50 °C during 64 h. In addition to the above three examples of achiral conjugated additions to β-nitrostyrene **3a**, two asymmetric additions by employing two different heterogenized catalyzes were demonstrated. Our group recently reported calcium-catalyzed enantioselective 1,4-addition of 1,3-dicarbonyl compounds to nitrostyrenes under continuous-flow conditions using polymer-supported Ca−Pybox.[20] Two sets of this chiral catalyst packed in column B4 of 100 mm length could be successfully used in the present two-step flow reaction; using dimethyl malonate (**7**) as a nucleophile, the corresponding γ-nitrodimethyl malonate derivative **14** was obtained in high yield with high enantioselectivity at 0 °C. Another pattern of heterogeneous chiral catalyst was an immobilized organocatalyst developed by Wennemers.[21] We synthesized H-D-Pro-Pro-Glu-εAhxPS, a supported peptide catalyst packed in column B5 according to the literature, and used it in our two-step flow system.[21] The 1,4-addition reaction of butanal (**8**) afforded the α-functionalized aldehyde (**15**) in high yield with high diastereo- and enantioselectivities, although the yield was slightly decreased, presumably because of the difference in solvent.[22] Functional-

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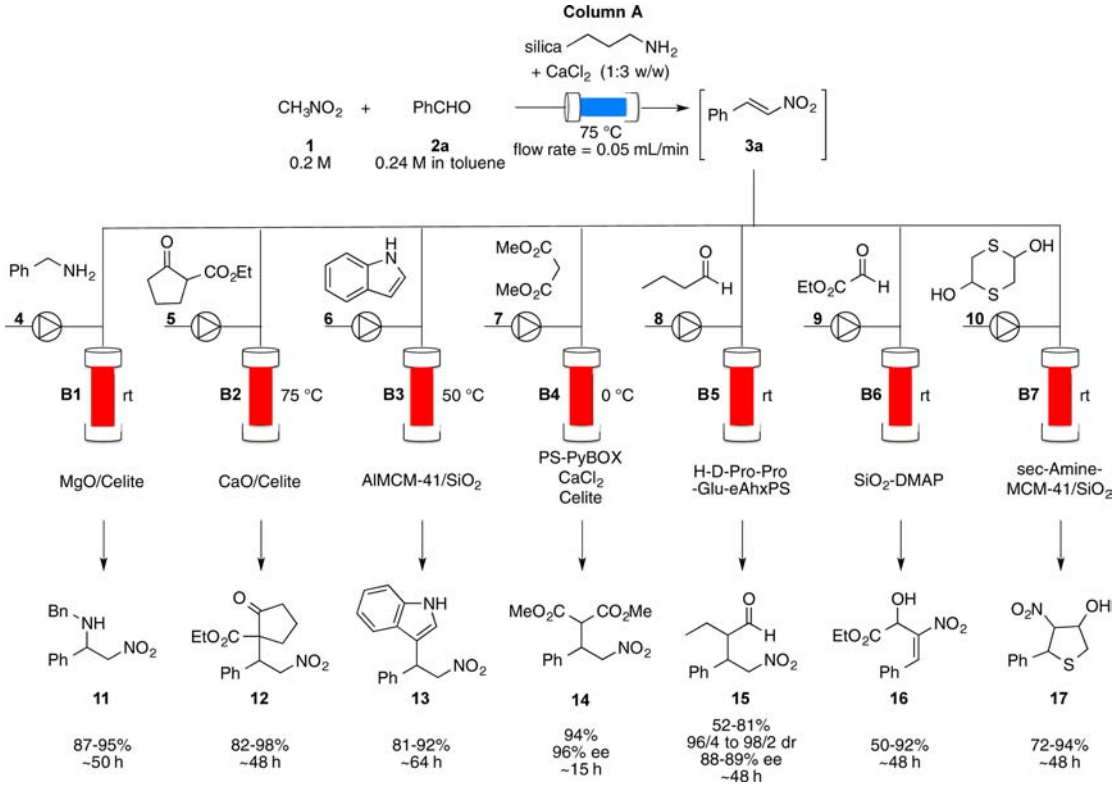
Scheme 4. Two-Step Continuous-Flow Reactions for Syntheses of Nitro-Containing Compounds

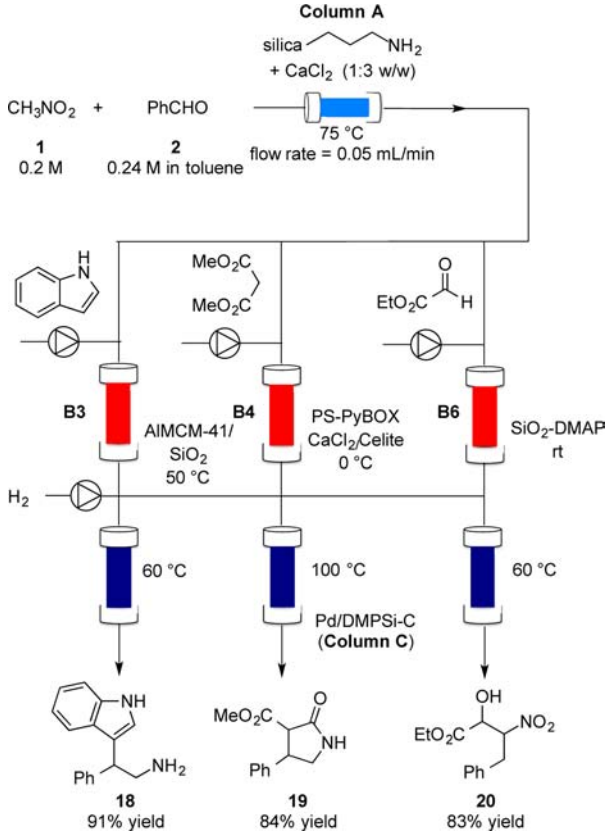


ization of the β-position of β-nitrostyrene was also possible using the Morita–Baylis–Hillman reaction with glyoxylate. Silica-immobilized *N*,*N*′-dimethylaminopyridine (DMAP)[23] was used as a catalyst packed in column B6. In this reaction, the desired compound **16** was obtained in high yield at an earlier stage (92% at 3 h, 85% at 15 h, and 80% at 19 h); however, the yield was gradually decreased to 50% after 48 h. β-Nitrostyrenes are also useful precursors for heterocyclic compounds, and several kinds of addition/cyclization reactions give heterocycles. A base-catalyzed tetrahydrothiophene synthesis was shown to prove the possibility;[24] secondary amine-functionalized aluminum-containing MCM-41 prepared from bis(3-trimethoxysilylpropyl)amine was used as a catalyst packed in column B7, and the desired tetrahydrothiophene **17** by the reaction with 2,5-dihydroxy-1,4-dithiane (**10**) was obtained in 75–94% yield during 48 h.

Some results shown in the present investigation offer obvious advantages over reported one-pot reactions among aldehydes, nitromethane, and active methylene compounds[16a,e,f] or indole[16f] in terms of yields and minimizing feed of reactants. These advantages are also observed compared with a sequential flow reaction consisting of nitrostyrene formation and 1,4-addition reported by Sartori et al., where solvent exchange from nitromethane to dichloromethane was required.[15] Moreover, the present continuous-flow systems have the potential to connect with the third and fourth flow systems. Examples of three-step continuous-flow reactions are shown in Scheme 5 in which three continuous transformations were successfully conducted with heterogeneous catalysts.

In summary, synthesis of β-nitrostyrene derivatives and the following derivatization reactions through two-step continuous-flow protocols with heterogeneous catalysts have been successfully carried out to demonstrate examples of fine organic synthesis in flow (flow fine synthesis[4]). According to this protocol, various heterogeneous catalysts, such as solid bases, immobilized bases, solid acids, and chiral supported

Scheme 5. Three-Step Flow Transformations



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metal and nonmetal catalysts in the second step are compatible with the catalyst in the first step and can provide useful intermediates with nitro groups that can be converted to amino and other functional groups. Moreover, the continuous-flow reactions developed here are environmentally benign and truly efficient for the preparation of nitro-containing compounds under safe conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00282.

Experimental details, effects of flow rates and concentrations, substrate scope of aldehydes; supporting results for two-step continuous-flow synthesis of nitro-containing compounds; NMR spectra and HPLC charts (PDF)

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Notes

The authors declare no competing financial interest.

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