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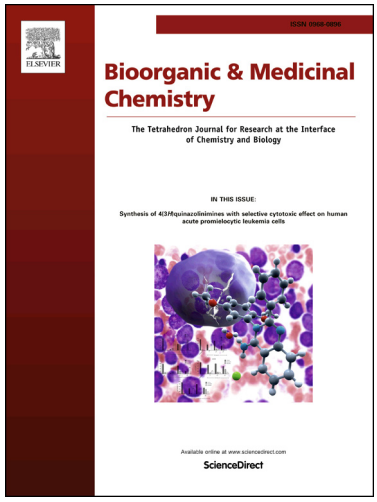

Continuous-Flow Synthesis Using a Column Reactor Packed with Heterogeneous Catalysts: A Convenient Production of Nitroolefins by Using Amino-Functionalized Silicagel

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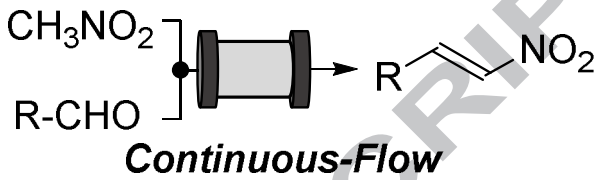

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ABSTRACT

A continuous-flow synthesis of β-nitroolefins by using heterogeneous base catalysts has been developed. Although the use of an excess amount of nitro-donor such as nitromethane is required in conventional methods, nearly equimolar amounts of nitro-donors and carbonyl compounds are sufficient for high-yielding production of nitroolefins. Catalysts for this flow protocol are inexpensive and abundant, and high durability and high productivity were also realized by using an appropriate second support.

1. Introduction

Continuous manufacturing of fine chemicals is one of the most important areas of current synthetic chemistry and chemical engineering.[1,2] For truly efficient continuous production of chemical materials, continuous-flow chemistry has become a powerful solution; the approach offers several benefits such as environmental compatibility, efficiency, and safety.[3–7] In addition to high value-added specialty chemical products such as APIs, mid-range valued fine chemicals such as common intermediates for the above valuable products can be produced in an sustainable way by employing continuous-flow techniques.[8, 9] To realize continuous-flow synthesis of nonspecialty chemicals, utilization of catalytic processes with inexpensive, abundant, and readily available heterogeneous catalysts is required for realistic prospects of commercialization.[10] Nitroolefins are one of the most important classes of nitrogen-containing intermediates.[11,12] They provide various types of nitro compounds through addition to carbon–carbon double bonds, and the nitro compounds that are obtained can be converted into a wide range of nitrogen-containing compounds including amines, amides, and lactams by applying further transformations.[13–15] For straightforward and systematic assembly of such chemical systems using key intermediates and another reactants, sequential flow reactions are an ideal approach; these systems provide several advantages over one-pot assembly in terms of selectivity and compatibility of substrates and/or catalysts.[16–21] Our group has focused on the application of heterogeneous catalysts for continuous-flow reactions.[20] Our recent efforts on sequential and continuous-flow asymmetric synthesis of (*R*)- and (*S*)-Rolipram[23] revealed that commercially available aminopropyl-functionalized silicagel was quite effective for the synthesis of nitrostyrenes from near equimolar amounts of aromatic aldehyde and nitromethane; however, a remaining challenge is the utilization of other aldehydes including aliphatic aldehydes as substrates for nitro-group acceptors. Nitroolefins including nitrostyrenes are usually synthesized by using either 1) a multistep reaction[24] involving condensation and dehydration reactions between a carbonyl compound and an excess of nitroalkane, or 2) a single-step reaction between these reactants catalyzed by supported amines,[16,25–29] a Lewis acid/amine system,[30] or an amino acid lithium salt,[17] and so on.[31-33] Major issues are the requirements for harsh reaction conditions and the large amount of nitro-donating substrate required. The use of an excess amount of nitromethane involves some particular difficulties with respect to the utilization of the product nitroolefins because of the need to remove the excess after the reaction, especially for continuous-flow conditions.[34] Moreover, the limited range of readily available nitroalkanes is a bottleneck for their use in such an approach. In this study, we have improved our packed-catalyst system for nitroolefination and expand the scope of the reaction with respect to the aldehyde to increase the versatility of the

method. In addition, our flow synthesis of nitroolefins is shown to be applicable for nitroalkane preparation through successive partial hydrogenation of carbon–carbon double bond moieties (Figure 1).

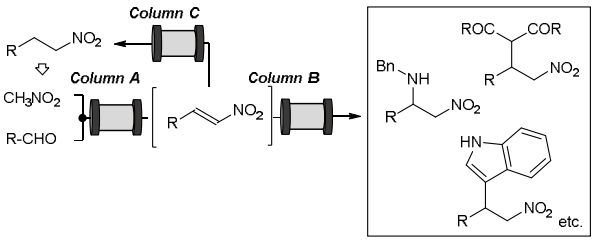
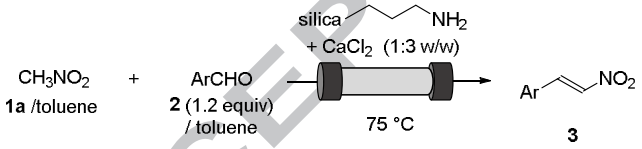


Figure 1. Nitroolefination and sequential use for various nitro-containing compounds.

2. Results and Discussion

2.1. Continuous-flow synthesis of nitrostyrenes

We began to investigate efficient and scalable production of β-nitrostyrene by examining the effects of flow conditions in the reaction of nitromethane (**1a**) with benzaldehyde (**2a**, Ar = Ph). A SUS column of 300 mm length and 10 mm diameter with column ends was filled with a mixed catalyst system consisting of commercially available primary amine-functionalized silicagel (AP-SiO_2; CHROMATOREX DM1020 NH®) and anhydrous calcium chloride (Scheme 1). Toluene solutions of the substrate mixture (**1a**/**2a** = 1:1.2) were fed by using a plunger pump at a 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. Conversions of **2a** at the point of 36 mmol of **1a** supplied to the catalyst column in eight experiments are plotted in Figure 2. It was shown that high concentration of substrates did not affect the conversion, although the application of a flow rate of >0.10 mL/min strongly suppressed the reaction. Clearly, sufficient productivity was secured by supplying 0.5 M substrate solution at 0.05 mL/min flow rate.



Scheme 1. Flow nitroolefination

With these flow conditions in hand, we then examined 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 above flow conditions. The yields of **3** remained at around 90% while more than 100 mmol of **1a** and 120 mmol of **2** were supplied, and the catalyst system was stable for more than 80–100 h. In the case of 2-thiophenecarboxaldehyde (**2e**), lower concentrations (0.3 M for **1a** and 0.36 M for **2e**) were required to secure good yields (Scheme 2).

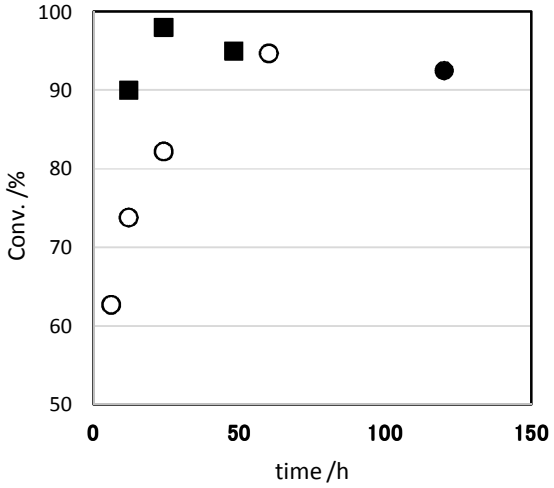
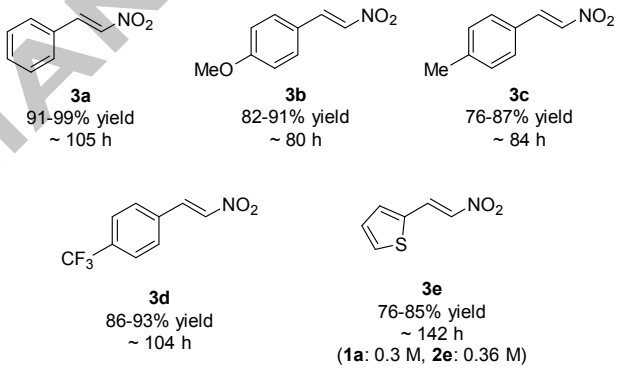


Figure 2. Time/conversion diagram for supplying 36 mmol of **1a** + **2a**. Note: Closed circle [0.1 M, 0.05 mL/min], closed square [0.2, 0.5, 1.0 M (from right to left) solution at 0.05 mL/min], open circle [with 0.1 M solution at 0.1, 0.25, 0.5, 1.0 mL/min (from right to left)].



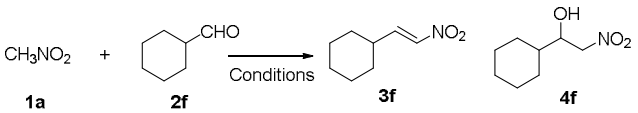
Scheme 2. Scope of the reaction with respect to the aromatic aldehyde.

2.2. Continuous-flow synthesis of aliphatic nitroolefins

Our focus then moved to the synthesis of aliphatic nitroolefins by using the present flow method. A preliminary investigation on such substrates highlighted some difficulties;[6] therefore, we reexamined the use of several solid bases that were suitable for the reaction of cyclohexanecarboxaldehyde (**2f**) with 1.5 equivalent of nitromethane (**1a**) at 50 °C under batch conditions (Table 1). The reaction in the presence of 200 mg/mmol of AP-SiO_2, which corresponded to 0.14 equivalent of NH_2 to the aldehyde, proceeded well to afford the dehydrated nitroolefin **3f** irrespective of the level of conversion, and the yield of **3f** at 12 h was 92% (entry 2). Typical solid bases such as CaO, KF supported alumina (KF/Al_2O_3), and anion-exchange resins (Amberlite) gave nitroaldol adduct **4f** predominantly (entries 3–5). Clearly, product **3f** in the AP-SiO_2-catalyzed reaction was not a sequential product that was formed via **4f** as an intermediate, and an aza-Henry pathway that proceeded through imine formation was strongly suggested. The ratio of AP-SiO_2 to the substrates was found to be crucial; the use of 150 mg/mmol of

AP-SiO_2 gave 80% yield (entry 6), whereas 100 mg/mmol of AP-SiO_2 resulted in a poor yield (entry 7). We then examined the use of suitable second supports. Whereas anhydrous calcium chloride gave 45% yield of **3f** (entry 8), the use of 4Å molecular sieves (MS4A) gave a better result (entry 9). Thus, our investigation on continuous-flow synthesis of aliphatic nitroolefin derivatives was conducted by using a catalyst column containing AP-SiO_2 and MS4A.

Table 1. Nitroolefination of aliphatic aldehyde **2f** by using heterogeneous base catalysts

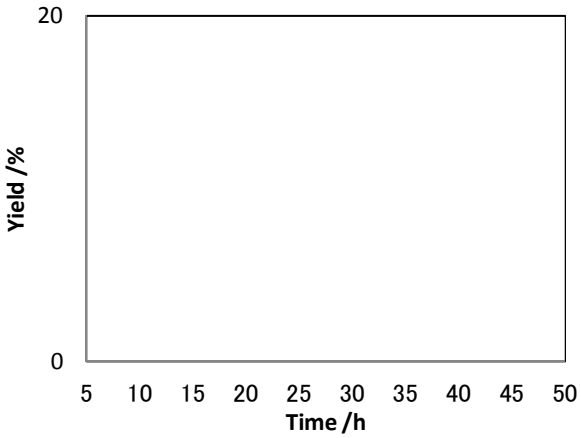


1a **2f** **3f** **4f**

entry	Catalyst	Conditions	Yield /%	
			3f	4f
1	AP-SiO_2 200 mg	50 °C, 3 h	54	trace
2	AP-SiO_2 200 mg	50 °C, 12 h	92	trace
3	CaO 200 mg	50 °C, 12 h	trace	99
4	KF/Al_2O_3 200 mg	50 °C, 12 h	21	78
5	Amberlite[a] 200 mg	50 °C, 12 h	trace	99
6	AP-SiO_2 150 mg	50 °C, 3 h	80	trace
7	AP-SiO_2 100 mg	50 °C, 3 h	4	Trace
8	AP-SiO_2 200 mg + $CaCl_2$ 200 mg	50 °C, 12 h	45	Trace
9	AP-SiO_2 200 mg + MS4A 200 mg	50 °C, 3 h	93	Trace

Continuous-flow direct nitroolefination of aliphatic aldehyde **2g** was conducted by using similar conditions to those used for the synthesis of nitrostyrene. A toluene solution of a mixture of **2g** (0.2 M), **1a** (0.3 M), and a GC internal standard was fed by using a plunger pump at a rate of 0.1–0.05 mL/min. We then examined the effects of the ratio of AP-SiO_2 and 4Å molecular sieves (Figure 3). By using a 1:1 (w/w) mixture of AP-SiO_2 and MS4A, the yield in the initial stage reached 90% (8 h) and gradually decreased to 70% (44 h). The 3:1 or 1:3 mixtures of AP-SiO_2 and MS4A did not give satisfactory yields and/or durability. Good levels of both yield and durability were even maintained with a 0.4/0.6 M mixture of substrates.

With these modified conditions in hand, we then expanded the substrate scope of the reaction with respect to carbonyl compounds as well as nitroalkanes (Scheme 3). Four kinds of aliphatic aldehydes including α- and β-branched derivatives and linear *n*-octanal worked well as nitro group acceptors to afford the corresponding nitroolefins in up to 96% yield at initial stages. The durability of the yield of the product depended on the substrates; 60–70% yields of the products were obtained in all cases for at least 44 h. The reaction between cyclohexanone and **1a** also proceeded to afford the corresponding allylic nitro compound **3j** in 86–88% yields during 70 h.[35] The reactions of 1-nitropropane with benzaldehyde gave the corresponding nitrostyrene **3k** in around 90% yield during 48 h, whereas the reaction with cyclopentanone with 1-nitropropane in lower yield. These nitroolefins are well recognized as precursors of γ-amino butyric acids (GABAs).[36,37] The present direct protocol using a short column and a plunger pump provides a clear advantage in terms of convenience, space saving, and atom economy over conventional two-step procedures.



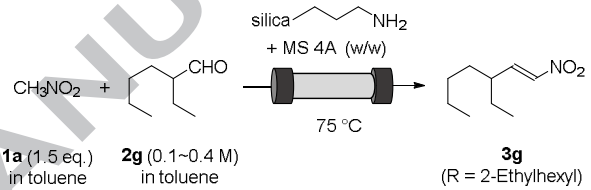
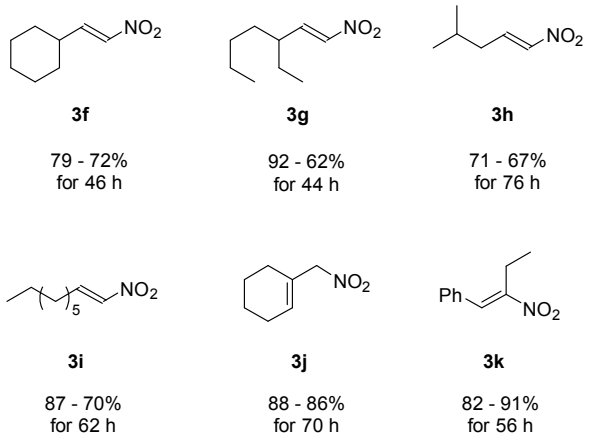


Figure 3. Effect of the amount of 4Å MS on flow synthesis of **3g**. Note: Closed circle (AP-SiO_2/MS4A = 1:1), open square (AP-SiO_2/MS4A = 3:1), closed triangle (AP-SiO_2/MS4A = 1:3).



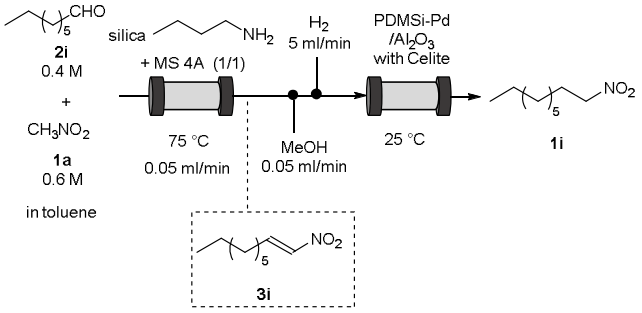
Scheme 3. Scope of the reaction with respect to aliphatic aldehyde. Typical conditions: **1a** or **1b** (0.6 M), **2** (0.4 M) in toluene; catalyst [AP-SiO_2 + MS4A (1:1 w/w) in 10 × 200 mm] column heated at 75 °C; flow rate, 0.05 mL/min.

2.3. Sequential continuous-flow reaction for nitroalkanes

Finally, we connected the present nitroolefination flow with a hydrogenation flow to examine the possibility of partial hydrogenation to afford the corresponding nitroalkane (Scheme 4). The functional group tolerance in nitroolefin hydrogenation has typically been secured through the stoichiometric use of metal hydride species, Hantzsch esters or FLPs.[38–40] The catalytic

processes of this reaction using molecular hydrogen as a hydrogen source are an unresolved task for chemoselective organic transformations. Here, we used a polysilane-alumina-based heterogeneous Pd catalyst developed by us previously.[41] A stream of nitroolefination furnishing **3i** (0.05 mL/min) was attached to a Y-shaped connector, and methanol was flowed from the other side at a rate of 0.05 mL/min. The resulting toluene–methanol solution of **3i** was introduced to a second column containing polydimethylsilane (PDMSi)-Pd/alumina and Celite (1:1) mounted with a hydrogen gas inlet. The desired hydrogenation proceeded smoothly at room temperature to afford the corresponding nitroalkane **1i** in good yield and with high product selectivity. The 60–70% yields of **1i** were reflected in the yield of nitroolefination, and the unreacted aldehyde **2i** from the first column was found; however, neither fully hydrogenated amine nor its intermediates were detected from the outlet.

Scheme 4. Two-step sequential flow reaction for synthesis of nitroalkane **1i**



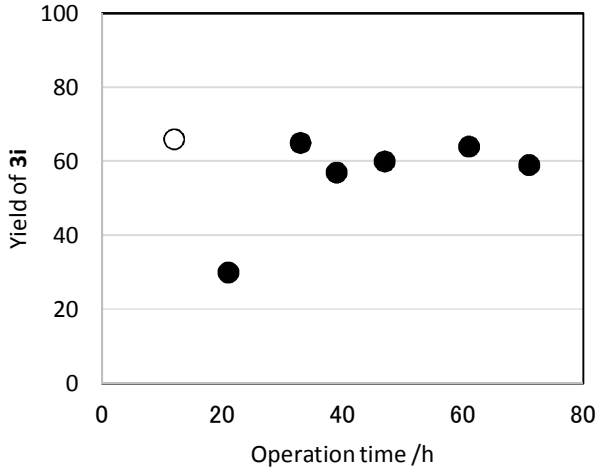


Figure 4 Time course of the two-step sequential flow reaction. Note: Open circle (yield of **3i** at 12 h), closed circle (yield of **1i**). The stream of **3i** was flowed to the next column at 15 h.

3. Conclusions

We have demonstrated an effective continuous-flow nitroolefination of aromatic and aliphatic aldehydes. By using this protocol, hydrocarbon scaffolds of aldehydes can be converted directly into nitroolefins accompanied by single-carbon homologation. The heterogeneous catalyst packed in the present column reactor is inexpensive and abundant, and the present system is space saving and can be operated safety. Partial hydrogenation of the resulting nitroolefins gives evolved nitroalkanes; thus, various types of nitroalkanes and nitroolefins will be accessible by using these techniques.

Acknowledgments

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