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Description	

Synthesis of *N*-Hydroxysuccinimide from Succinic Acid and Hydroxylammonium Chloride using Amberlyst A21 as Reusable Solid Base Catalyst

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Abstract. Solid base catalysts were studied for the first time to synthesize *N*-hydroxysuccinimide (NHS) through the reaction of succinic acid with hydroxylammonium chloride. The highest yield of 42% ($\pm 3\%$) with 65% ($\pm 4\%$) selectivity toward NHS production was achieved by using Amberlyst A21, which is a weak base anion-exchange resin. The present catalyst could be recycled during five runs without significant decreases in activity. Also, efficacy for the Amberlyst A21 mediated reaction was also explored with other dicarboxylic acids such as phthalic acid, glutaric acid, and maleic acid.

Keywords. *N*-hydroxysuccinimide, succinic acid, hydroxylammonium chloride, solid base catalyst

INTRODUCTION

Cyclic *N*-hydroxyimides are versatile compounds which are widely used in peptide synthesis [1], aerobic oxidation [2-4], and polymerization [5, 6]. Particularly, *N*-hydroxysuccinimide (NHS, **Fig. 1**) is a valuable intermediate in the formation of activated ester derivatives for coupling reactions with amino acids, peptides, or their esters [7].

Conventionally, cyclic *N*-hydroxyimide compounds are prepared by the reaction of dicarboxylic anhydrides with hydroxylammonium salt as a reagent. It is claimed that utilization of dicarboxylic acid form as a raw material is not favorable regarding reaction kinetics [8] and its stability; *i.e.*, it is quickly deactivated by the acid-base reaction [9]. Therefore, seeking a process that employs dicarboxylic acids as a starting material avoiding the step of converting them into corresponding dicarboxylic anhydrides is essential.

A U.S. patent disclosed a method to produce NHS in a good yield (95%) from succinic acid [10]. However, the reaction system is complicated as it requires a Dean-Stark apparatus, a solvent capable of forming a dehydration-condensation product with hydroxylamine and an azeotropic solvent. Furthermore, a stoichiometric amount of a deprotonating base was involved in treating with hydroxylammonium chloride, which causes the formation of salt waste during the synthesis. It is worth noting that using free hydroxylamine requires deliberate manipulation due to its explosive nature. Therefore, hydroxylamine salts are generally employed. Another U.S. patent reported a process to synthesize *N*-hydroxyphthalimide (NHPI, 86%) in water solvent without the

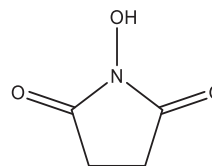


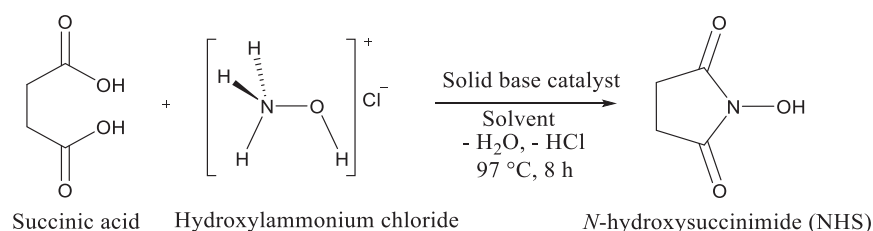
FIGURE 1. Structure of *N*-hydroxysuccinimide (NHS).

addition of a base. This simple method, however, requires elevated temperature reaction (130 °C) and an excessive amount of phthalic anhydride to hydroxylammonium phosphate (approx. 3 equiv) [9].

The use of solid base catalysts is continuously expanding because of its many advantages regarding economic and environmental problems compared to that of liquid bases [11]. Along with the development in solid base catalysts, more recently, resin-bound catalysts have been becoming more and more important in organic synthesis due to their recyclability, ease of separation and purification, and higher safety feature against potential explosive reagents [12]. Many kinds of ion-exchange resins, namely Amberlyst, Amberlite, and Dowex are now available at low cost, the greater diversity of functionalities, and higher loading capacities [13].

Amberlyst A21 is a weakly basic anion-exchange resin containing $N(CH_3)_2$ functional group and water moisture (56-62%) [14-16], and its high catalytic activity, selectivity, and excellent stability for the Henry reaction, Michael reaction, and transesterification reaction were explored [17-20]. Because the Amberlyst A21 possessed various important performances such as *i*) the less susceptibility to organic pollutants, *ii*) more resistance to oxidation, hydrolysis and elevated temperature, and *iii*) excellent sorption capacity, and *iv*) recyclability, it has also been applied for various applications in waste treatments such as removals of chromates and azo dyes [21, 22].

Herein, to overcome the drawbacks from the previous methods on the NHS synthesis, this paper addresses the production of NHS by carrying out a reaction between succinic acid and hydroxylammonium chloride in the presence of catalytic amount of a solid base. Several catalysts and solvents were examined along with the optimization of reaction conditions and other contributed factors (**Scheme 1**).



SCHEME 1. Synthesis of NHS with succinic acid and hydroxylammonium chloride over solid base catalyst.

EXPERIMENTAL

Chemicals

Succinic acid, potassium carbonate, magnesium oxide, acetonitrile, phenolphthalein, dimethyl sulfoxide (DMSO), acetic acid, and dimethylformamide (DMF) were supplied by Kanto Chemical Co., Inc. Phthalic acid, hydroxylammonium chloride, toluene, benzoic acid, 1,4-dioxane, *N*-hydroxysuccinimide, ethanol, and formic acid were purchased from Wako Pure Chemical Ind. Ltd. Glutaric acid, Amberlyst A21, and *N*-hydroxyphthalimide were provided by Sigma Aldrich Japan. Amberlyst A26, Mg-Al hydrotalcite, and maleic acid were obtained from Dow Chemical Co., Tomita Pharmaceutical Co. Ltd., and Tokyo Chemical Ind. Ltd., respectively.

Typical procedures for reaction, analysis, and recycling

The reaction was carried out in a 20-mL round-bottom flask with a reflux condenser. The flask was charged with succinic acid (1 mmol), hydroxylammonium chloride (1.25 mmol), catalyst (0.5 g), and solvent (5 mL), and then the flask was immersed in an oil bath, which was held at 97 °C and 400 rpm. Heating was terminated after 8 hours and cooled to room temperature before analyzing.

For high-performance liquid chromatography (HPLC) analysis, formic acid (100 μ L) was added into the analyte as an internal standard, and then distilled water (16 mL) was added to dissolve the remaining reactants and product. The obtained water phase (1 mL) was then withdrawn and diluted with water (10 mL) before analyzing by HPLC (Column: Shodex RSpak DE-413L; Detector: RID-10A; Buffer solution: 10 mM H_3PO_4 , 1.0 mL/min, 323 K). While, for proton nuclear magnetic resonance (1H -NMR), the analyte was dissolved in

dimethyl sulfoxide- d_6 (DMSO- d_6) and analyzed by the Bruker Avance III, 400 MHz. Maleic acid (Purity = 99%) was used as an internal standard in the case of $^1\text{H-NMR}$ analysis.

To examine the recyclability of the solid catalyst, the used catalyst was recovered by simple filtration and washed with water. After that, it was treated with 2% NH_3 (2 mL) at room temperature in 1 h, followed by treating with water (2 mL) in an oven at 80 °C for 1 h.

Isolation procedure

N-hydroxyphthalimide, which was obtained by the reaction of phthalic acid and hydroxylammonium chloride, was isolated by crystallization method. After the reaction, toluene was removed by pipette filtration. A minimum amount of hot distilled water was added to the reaction flask to dissolve the product. The catalyst was then separated by simple filtration, and the filtrate was cooled at room temperature. After 2 h crystallizing, all the yellowish crystals formed were filtered and dried in vacuum to give the final product with the yield of 34%.

RESULTS AND DISCUSSION

To select an effective catalyst for the target reaction, several solid bases were compared their reactivities in toluene solvent. The results are summarized in **Table 1**. It is noticeable that among different kinds of catalysts, only Amberlyst-types rein catalysts named as Amberlyst A21 and Amberlyst A26 showed activities to the reaction. In detail, the former catalyst could give the highest yield and selectivity of 42% ($\pm 3\%$) and 65% ($\pm 4\%$), respectively, while those of the latter are lower at 26% and 54% (entries 1 and 2). All the remaining catalysts (MgO, Mg-Al hydrotalcites, and K_2CO_3) did not have any activity for the reaction (entries 3-6).

TABLE 1. Effect of catalyst^[a]

Entry	Catalyst	Conv. /%	Yield /%	Sel. /%
1	Amberlyst A21	65	42	65
2	Amberlyst A26	48	26	54
3	MgO	0	0	0
4	Hydrotalcite (Mg/Al = 5.4)	0	0	0
5	Hydrotalcite (Mg/Al = 3.02)	0	0	0
6	K_2CO_3	0	0	0

[a] Reaction conditions: succinic acid (1 mmol), hydroxylammonium chloride (1.25 mmol), toluene (5 mL), reaction temperature (97 °C), reaction time (8 h), stirring speed (400 rpm).

The base amount of Amberlyst A21 is 0.1 mmol/g, which was measured by titration method using benzoic acid (0.05 M) as a titrator and phenolphthalein (0.05 %wt.) as an indicator. Turn over number (TON) of the reaction was then calculated as described in **Eq. 1**. This TON value is over than 1, indicating that Amberlyst A21 proceeded the synthesis of NHS, catalytically.

$$\text{TON} = \frac{\text{Mole of desired product formed}}{\text{Base amount}} = \frac{0.42}{0.05} = 8 \quad (\text{EQUATION 1})$$

The catalyst amount was also optimized by varying it from 0 to 0.8 g of Amberlyst A21 (**Table 2**). It was seen that without the catalyst, the reaction did not proceed at all (entry 1). Whereas, the yield of the product increased along with the rise of catalyst amount from 0.1 g to 0.5 g (entries 2-4). Notably, the further addition amount to 0.8 g of catalyst even had an adverse effect on the reaction as it made a significant decrease to 19 % in yield of NHS (entry 5).

TABLE 2. Effect of amount of Amberlyst A21^[a]

Entry	Amount /g	Base amount /mmol	Conv. /%	Yield /%	Sel. /%
1	0	0	0	0	0
2	0.1	0.01	13	9	69
3	0.3	0.03	49	33	67
4	0.5	0.05	65	42	65
5	0.8	0.08	54	19	35

[a] Reaction conditions: succinic acid (1 mmol), hydroxylammonium chloride (1.25 mmol), toluene (5 mL), reaction temperature (97 °C), reaction time (8 h), stirring speed (400 rpm).

The effect of solvents on the efficiency of the catalyst was then examined, and the results are shown in Table 3. Among three kinds of solvents, which are classified by their polar properties, the non-polar solvents were the most suitable for the reaction (entries 1 and 2). The polar-protic and polar-aprotic solvents were less effective (entries 3, 4, 6) or failed to give the product (entries 5, 7, 8).

TABLE 3. Effect of solvents^[a]

Entry	Solvent	Polarity	Conv. /%	Yield /%	Sel. /%
1	Toluene	Non-polar	65	42	65
2	1,4-dioxane		19	15	79
3	Water	Polar-protic	10	3	30
4	Acetic acid		4	4	100
5	Ethanol		0	0	0
6	Acetonitrile	Polar-aprotic	7	3	43
7	DMSO		0	0	0
8	DMF		0	0	0

[a] Reaction condition: succinic acid (1 mmol), hydroxylammonium chloride (1.25 mmol), Amberlyst A21 (0.5 g), solvent (5 mL), reaction temperature (97 °C), reaction time (8 h), stirring speed (400 rpm).

To optimize the reaction time, a series of experiments were carried out, viz. 1h, 4 h, 8 h, 12 h and 24 h. Fig. 2 describes a considerable increase in yield as changing from 1h to 8h of reaction time. Keeping the reaction for a more extended period than 8 h, however, not only showed a modest increase in yield but also led to a drop in selectivity.

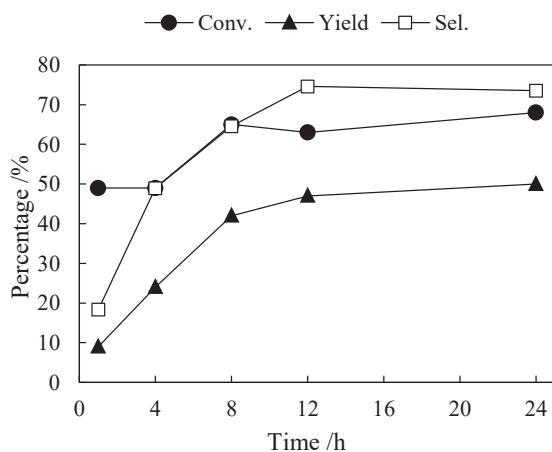


FIGURE 2. Time course of the reaction

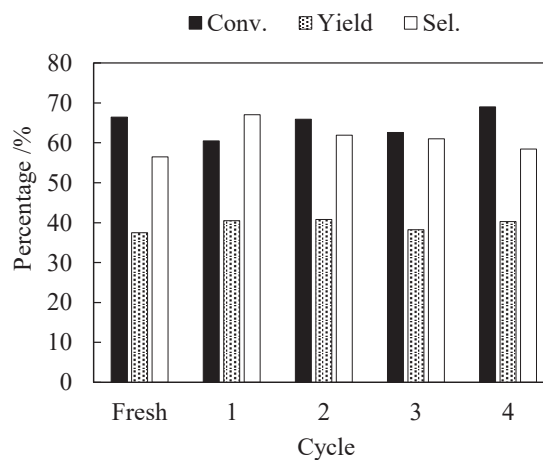
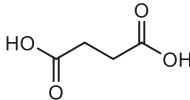
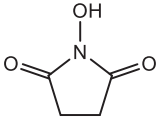
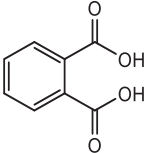
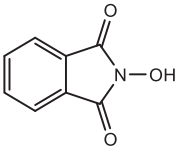
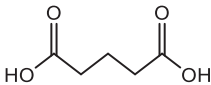
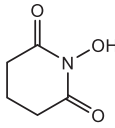
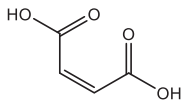
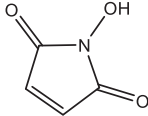


FIGURE 3. Catalyst recyclability

Finally, the catalyst was tested to evaluate its stability and recycling capabilities (**Fig. 3**). It was observed that the catalyst could keep its efficiency for at least 5 runs without any significant loss in conversion and selectivity.

Having optimized the reaction parameters such as catalyst, catalyst amount, solvent, reaction time, the efficiency of the ideal protocol was tested for the reaction of other dicarboxylic acids such as phthalic acid, glutaric acid, and maleic acid. The results described in **Table 4** showed that in case of phthalic acid, *N*-hydroxyphthalimide was also successfully synthesized and gave an isolated yield of 34% with high purity (entry 2). A low yield of only 6% was obtained in case of glutaric acid (entry 3), while the reaction with maleic acid was failed to give the desired product (entry 4).

TABLE 4. Substrate scope^[a]

Entry	Dicarboxylic acid	Product	Yield /%
1	 Succinic acid	 <i>N</i> -hydroxysuccinimide	42 ^[b]
2	 Phthalic acid	 <i>N</i> -hydroxyphthalimide	34 ^[c]
3	 Glutaric acid	 <i>N</i> -hydroxyglutarimide	6 ^[d]
4	 Maleic acid	 <i>N</i> -hydroxymaleimide	0

[a] Reaction conditions: dicarboxylic acid (1 mmol), hydroxylammonium chloride (1.25 mmol), Amberlyst A21 (0.5 g), toluene (5 mL), reaction temperature (97 °C), reaction time (8 h), stirring speed (400 rpm).

[b] HPLC yield

[c] Isolated yield, 24 h of reaction period, purity = 97%

[d] NMR yield

CONCLUSION

In summary, Amberlyst A21 was found to be a potential recyclable solid base catalyst for the synthesis of *N*-hydroxysuccinimide from the reaction of succinic acid with hydroxylammonium chloride in toluene solvent. The optimized conditions were applied for the reaction with other 3 dicarboxylic acids. However, only an acceptable yield of *N*-hydroxyphthalimide was obtained from phthalic acid.

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