CLEAN AND EFFICIENT SYNTHESIS OF *N*-ARYL AND *N*-ALKYL SUCCINIMIDES IN SUB-CRITICAL WATER

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In this study, we propose an alternative, fast and clean method using sub-critical water. First, we found that the reaction of succinic acid with aniline occurred rapidly in water at 280ºC in 30 min with 72% yield. The reaction of succinic acid with alkyl amines was also investigated, as well as anilines. The literature doesn't mention any example of succinimide synthesis in sub-critical water.

INTRODUCTION

The development of simple and general synthetic routes for widely used organic compounds from readily available reagent is one of the major challanges in organic synthesis. Imide derivatives are among such types of organic compounds with numerous applications in biology and synthetic chemistry (1,2). Thus, *N*-aryl and *N*-alkyl succinimides have been examined as potential fungicides, especially *N*-(3,5-dichlorophenyl) succinimide. The 3-hydroxy derivatives are involved in their metabolic pathways (3). Some of them show activities as aminopeptidase *N* inhibitors. Despite their wide applicability, routes available for the synthesis of imide derivatives are limited. These syntheses usually start from the anhydride and give the corresponding amic acid, followed by cyclization under acidic conditions (4)

Green and sustainable chemistry, a new concept that arose in the early 1990s, gained wider interest. Green and sustainable chemistry concerns the development of processes and technologies that result in more efficient chemical reactions that generate little waste and fewer environmental emissions than "traditional" chemical reactions do. The use of water as solvent for organic reactions is one of the finest solutions to the problem of solvent toxicity and disposal. The chemistry in natural systems (biochemical reactions) is based on water. The use of water as solvent for synthetic chemistry holds great promise for the future in terms of the cheaper and less hazardous production of chemicals. Researchers in this area are discovering that reactions in water may be predisposed to favor transition states that optimize hydrophobic interactions, thereby achieving unusual, unique selectivity in organic reactions (5).

Sub-critical water has many advanteges over the usual organic solvents. It is efficiently one of the cheaper solvent and so one of the most economic. It is also safer than the usual organic solvents. From an industrial point of view, the use of a two-phase system allows an easy separation of the products from water. Finally, water is environmentally friendly and could obviously diminish the problems of pollution by organic solvents.

In this study, we propose an alternative, fast and clean method using sub-critical water with short reaction times. Although reaction of aliphatic amines needs more investigation, it's possible to say that the reaction is general and applicable to aliphatic amines and aromatic amines. The literature doesn't mention any example of succinimide synthesis in sub-critical water. Once again, other examples of synthesis of succinimides in organic solvents, uses succinic anhydride as starting material and with two steps to obtain target succinimide from succinic anhydride.

MATERIALS AND METHODS

Materials. Succinic acid; aniline; 2,5-dichloroaniline; propane-1-amine ; butane-1-amine ; hexane-1-amine are all analytical reagent grade and were obtained from Merck. All materials were used as received.

Experimental Procedure. Reactions were typically carried out at 280 C with 1:20 mol ratio of substrat and amine. First, the system was purged with high-purity nitrogen. A certain amount of succinic acid and amine were added to the reactor, together with 10 mL of degassed deionized water. After the temperature inside the reactor had reached the reaction temperature, reactions were carried out for 30 min. The pressure during the reaction depend on the substrats. After the reaction the reactor were removed from heater and cooled down quickly in an ice bath. The reactor contents were extracted with ether (6x3mL) and analyzed using Thermo-Finnigan GC-FID and GC-MS.

Analysis

Reaction products were identified by Finnigan-Trace GC–MS equipped with an auto sampler and quantative analysis was carried out by Finnigan-Trace GC- FID. One microlitre of sample volume was injected using split method with 50 split ratio. Chromatographic separations were accomplished with a Zebron ZB-5 capillary column (5% phenyl–95% dimethylpolysiloxane, 0.25mm i.d.×60 m, film thickness 0.25 _m). Analysis was carried out using helium as the carrier gas, flow rate 1.0 mL/min. The column temperature was programmed from 50 to 280 °C at 5°C/min with hold 10 min at 280°C. The injection port temperature was 250°C. The ionization voltage applied was 70 eV, mass range *m*/*z* 41–400 a.m.u. The separated components were identified tentatively by matching with GC–MS results of National Institute of Standards and Technology (NIST) mass spectral library data because their reference reagent were not available.

Mass spectral analysis of the products

N-phenylsuccinimide **3** : 175 (M+, 25), 147 (20), 119 (100), 104 (20), 93 (70), 77 (50)
N-(2,5-dichlorophenyl)succinimide **5** : 243 (M+ 30) 247 (M+2, 10), 172 (25), 150 (10), 146 (30), 119 (100), 104 (20), 93 (70), 77 (50)
N-propylsuccinimide **7a** : 141 (M+, 35), 126 (15), 113 (50), 100 (100) , 84(25), 72 (15), 55 (45)
N^1,N^4-dipropylsuccinamide **7b**: 200 (M+ 30), 142 (100), 114 (70), 100 (75), 72 (45), 58 (50)
N-butylsuccinimide **9a** : 155 (M+, 35), 140 (5), 126 (15), 113 (50), 100 (100) , 84(25), 72 (15), 55 (45)
N^1,N^4-dibutylsuccinamide **9b** : 228(M+, 30); 186 (60), 156 (100), 128 (70), 100 (80), 72 (75), 57 (55)

N-hexylsuccinimide **11a** : 183 (M+, 30), 168 (35), 155 (40), 140 (15), 126 (20), 113 (50), 100 (100) , 84(25), 72 (15), 55 (45)
N^1,N^4-dihexylsuccinamide **11b** : 256 (M+, 25), 228 (30); 186 (60), 156 (100), 128 (70), 100 (80), 72 (75), 57 (55)

RESULTS

First, we found that the reaction of succinic acid **1** with aniline **2** occurred rapidly in water at 280ºC in 30 min with 72% yield. The optimum amount of water was found as 10 ml affording the product in good yield. Moreover, the reaction carried out with different ratios of substrats. The employment of a large excess of amines in the reaction also afforded the product in good yield. The optimized conditions were achieved using 1:20 ratios of succinic acid to amine. Once the optimized conditions were estimated, reactions extended to alkyl amines and substituted anilines to explore the generality of this green system and the results are summarized in Table 1.

A number of primary alkyl amines, aniline and activated anilines were smoothly converted to the corresponding *N*-substituted 2,5-pyrrolidiones without any catalyst within 30 min (figure 1 and figure 2). The results are summarized in Table1. As can be seen, the reactions of anilines with succinic acid carried out in sub-critical water conditions exhibit relatively higher conversions without any byproducts. The required reaction time was 30 min for all experiments. While the yield of *N*-phenyl- 2,5-pyrrolidione **3** was 72%, from the reaction of succunic acid **1** with 2,5-dichloroaniline **4**, a similar yield (68%) was obtained (entry 2 in Table 1). In the case of reactions with 2-nitroaniline and 4-nitroaniline, the reaction activity effected by substituents on the aromatic ring. Since, more electron withdrawing groups reduce the basicity of anilines, 2-nitroaniline; 4-nitroaniline were unsuccessful for *N*-substituted succinimide synthesis.

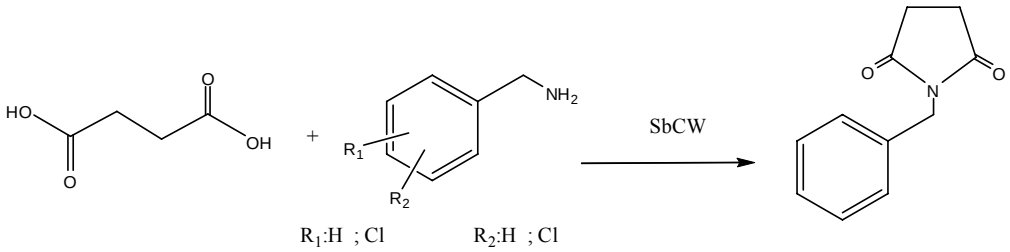
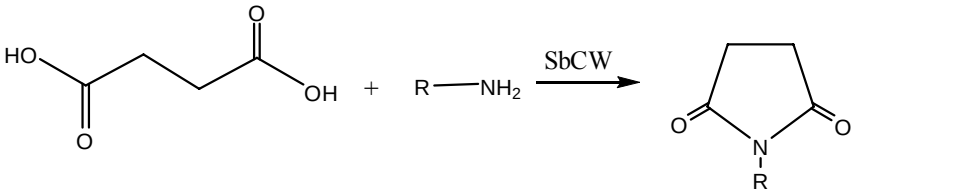


Figure 1 : Reactions of succinic acid and anilines in SbCW

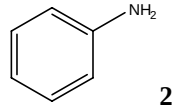
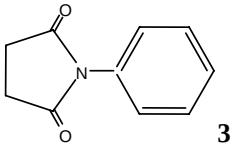
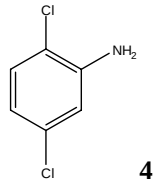
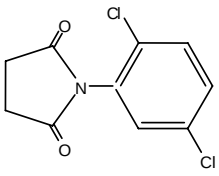
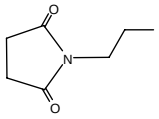
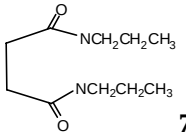
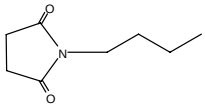
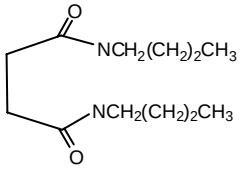
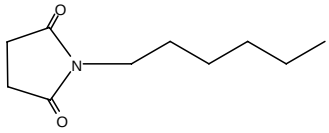
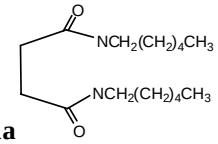
To check the behaviors of a typical aliphatic amine, a number of alkyl amines were also used. Unexpectedly, the N^1,N^4-dialkyl succinamides was observed as major product with *N*-alkylsuccinimides. These products were also prepared within 30 min. **7a** and **7b** (entry 3 in Table 1) was prepared with 82% total yield. N^1,N^4-dipropylsuccinamide **7b** was obtained in 50% while N-propylsuccinimide **7a** was obtained in 32%. Two products of reaction of butylamine **8** with succinic acid **1** were **9a** and **9b**. As could be seen from Table 1 the yield of N^1,N^4-dibutylsuccinamide **9b** (60%) is higher than those succinimide derivative **9a** (22%). Unfortunaly with a longer chained alkylamine **10** product yield of succinimide derivative was gained lower (product **11a** 20%). This can be explained with more basicity of hexylamine than those of shorter chained ones. On the other side, total conversion of alky amines into succinimide derivatives was very satisfactory.



R: $CH_3CH_2CH_2$; $CH_3CH_2CH_2CH_2$; $CH_3(CH_2)_4CH_2$

Figure 2 : Reactions of succinic acid and primery alkylamines in SbCW

Table 1 : Results of the reactions between succinic acid and various amines in SbCW

Entry	Amine	Product	Yield (%)
1	 **2**	 **3**	72
2	 **4**	 **5**	68
3	$CH_3CH_2CH_2NH_2$ **6**	 **7a**  **7b**	32 (**7a**) 50 (**7b**)
4	$CH_3(CH_2)_2CH_2NH_2$ **8**	 **9a**  **9b**	25 (**9a**) 60 (**9b**)
5	$CH_3(CH_2)_4CH_2NH_2$ **10**	 **11a**  **11b**	20 (**11a**) 62 (**11b**)

CONCLUSION

N-substituted succinimide synthesis is gained smoothly in SbCW without using any catalyst. Proposed method is faster and cleaner than conventional methods since using succinic acid instead of succinic anhydride hence avoids more reaction steps. Although reaction of aliphatic amines needs more investigation, it's possible to say that the reaction is general and

applicable to aliphatic amines and aromatic amines for succinimide synthesis. The literature doesn't mention any example of succinimide synthesis in sub-critical water.

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