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Solid-Phase Synthesis of *N*-Aryl Succinimides

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Abstract: A new method upon adopting a solid-phase strategy for synthesis of *N*-aryl succinimides is described here, using the silica-bound benzoyl chloride (SBBC) as dehydrating agent in reaction with *N*-arylsuccinamic acids. The main advantage of this method is the recyclability of SBBC.

Keywords: Silica-bound benzoyl chloride, solid-phase synthesis, succinimide

Over the past two decades, solid-supported chemistry has generated much research by chemists who are creating environmentally benign synthetic methods using easily separable and recyclable solid reagents.[1–7] These methods are usually ecofriendly because the solid-supported reagents can be recovered and reused several times. Solid-phase organic synthesis has commonly been used in combinatorial synthesis for generating libraries, and has often been used with high-throughput screening in modern medicinal chemistry for discovering new drugs.[8,9] Besides the properly functionalized organic polymers,[10] silica gel–grafted reagents have also been devised in some solid-phase organic syntheses.[11–13] Compared with organic polymers, silica gel is more robust to fairly drastic conditions and harsh reagents.

Herein we introduce silica-bound benzoyl chloride (SBBC) as a novel and efficient means for performing the cyclodehydration of *N*-arylsuccinamic acids **2a–g** to provide *N*-aryl succinimides **4a–g**. Succinimides and their congeners, pyrrolidines and pyrrolidone compounds, have been identified as the constituents of a wide array of natural and bioactive

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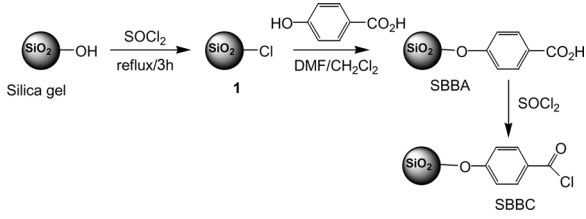
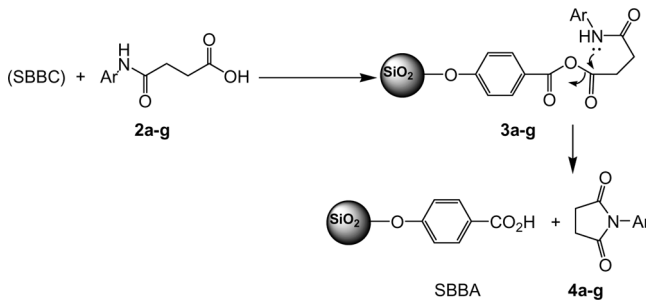
molecules.[14,15] Succinimides have gained numerous applications in different fields.[16] In medicine, they have been used for the treatment of arthritis, tuberculosis, convulsion, and epilepsy. In addition, they are the shared structural feature of compounds that show histone deacetylase inhibitory effects,[17] irreversible protease inhibitory effects,[18] and 5-HT1A and 5-HT2A receptor-affinity-producing antidepressant effects.[19] They have been used as valuable precursors in the synthesis of natural and synthetic organic molecules.[20–22] Partial or complete reduction of succinimides has frequently been exploited for production of pyrrolidinone and pyrrolidine-embedded alkaloides.[15,23,24] These fascinating features justify the contributions allocated to development and modification of the synthesis of succinimides.[25] Moderate yields of succinimides were directly obtained from complete condensation of primary amines with succinic anhydride at greater temperatures, ca. 180°C.[14,16] However, a popular route for the synthesis of succinimides involves partial condensation of a primary amine with succinic acid or anhydride at temperatures less than 100°C followed by cyclodehydration of the formed *N*-arylsuccinamic acids. Several dehydrating reagents such as acetic anhydride,[19,22,23] acetyl chloride,[15] and cyanuric chloride[26] were conventionally employed in this approach. However, use of these dehydrating agents usually suffers from difficulties encountered in their handling, separation, and recovering after reaction, therefore sometimes creating waste. To surmount these disadvantages, we intended to design and evaluate SBBC for cyclodehydration of *N*-arylsuccinamic acids **2a–g**. Accordingly, it is introduced here as an efficient and recyclable dehydrating agent for a convenient synthesis of succinimides.

As is depicted in Scheme 1, our approach to the synthesis of SBBC consists of three steps. In this course, we started from a known reaction between silica-gel powders and thionyl chloride to obtain the silica chloride **1**.[27–31] On reaction with 4-hydroxybenzoic acid in refluxing dichloromethane–dimethylformamide (8:1), this compound has provided SBBA. Conversion of SBBA to the desired acid chloride (SBBC) was readily attained by refluxing it in thionyl chloride. To the best of our



Scheme 1. Preparation of SBBC.



Scheme 2. A plausible mechanism for synthesis of succinimides **4a–g**.

knowledge, there is no report on the preparation and use of SBBC in any synthetic procedure. In comparison with commonly used acid chlorides such as acetyl chloride and benzoyl chloride, which are more hygroscopic and difficult to handle, SBBC can be used simply and stored more safely. In addition, SBBC is not wasteful to the environment because it is readily recovered after reaction and can be reused several times.

SBBC was mixed with each *N*-arylsuccinamic acid **2a–g** and then refluxed in dichloromethane (Scheme 2). The progress of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate–petroleum ether as eluent. After completion of the reaction, the hot slurry of the reaction mixture was filtered to separate the SBBA residue. The SBBA residue was washed with dichloromethane and recovered by refluxing it in thionyl chloride.

To optimize the required amount of SBBC, the reactions with two reactants, *N*-phenylsuccinamic acid **2a** and *N*-(4-methoxyphenyl)succinamic acid **2b**, were chosen as models. Table 1 summarizes the yields of relevant succinimides **4a,b** obtained using different amounts of SBBC in model reactions.

Table 1. Optimization of the amount of SBBC needed in the reaction with 1 mmol of substrate

Product	Ar	Amount of SBBC used (g)	Yields (%)
4a	Ph	0.6	70
4a	Ph	0.8	78
4a	Ph	1	78
4b	4-MeO · C_6H_4	0.6	73
4b	4-MeO · C_6H_4	0.8	83
4b	4-MeO · C_6H_4	1	83

Table 2. Results of reaction between **2a–g** and SBBC

Product	Ar	Reaction time (min)	Yields (%)	Mp (°C)	Lit. mp (°C)
4a	Ph	40	78	155–156	157[32]
4b	4-MeO·C_6H_4	30	83	160–162	—
4c	4-Cl·C_6H_4	55	71	164–165	167[32]
4d	4-Et·C_6H_4	30	88	137–138	—
4e	3-Me·C_6H_4	40	79	110–111	—
4f	4-Me·C_6H_4	30	83	152–154	154[32]
4g	4-EtO·C_6H_4	30	84	153–155	155[32]

According to the results of these optimization reactions, 0.8 g of SBBC was used in the reaction with 1 mmol of each *N*-aryl succinamic acid, and the relative products were obtained in good yields (Table 2). Also, it is interesting to note that under similar conditions and reaction times, the treatment of *N*-aryl succinamic acids with silica chloride **1** has not furnished the relative succinimides.

Furthermore, to investigate the recoverability of SBBC, three model reactions were chosen. After completion of each model reaction, the solid support was separated by filtration, washed with dichloromethane, dried in an oven, and then refluxed in excess thionyl chloride. The recovered SBBC was subjected to the next run of the reaction process with the same substrate. The results of the first experiment and subsequent experiments were almost consistent in yields after three runs (Table 3).

A reasonable mechanism for the formation of succinimides **4a–g** is indicated in Scheme 2. This mechanism involves the formation of putative mixed anhydride **3a–g**, which undergo thermal cyclo-elimination through intramolecular nucleophilic substitution of the nitrogen atom in favor of producing succinimide and leaving SBBA. As is apparent in

Table 3. Results of reusability of SBBC in model reactions

		Yields (%) of reaction from successive run with recovered SBBC		
Product	Ar	First use	First recovery	Second recovery
4b	4-MeO·C_6H_4	83	81	80
4c	4-Cl·C_6H_4	71	69	66
4g	4-EtO·C_6H_4	84	82	81

Table 2, substrates having electron-donating groups in the *para* position to the nitrogen substituent gave better yields under the reaction conditions. This result clearly shows a direct dependence of reaction kinetics on electron density at the nitrogen atom and therefore its nucleophilic character. To this end, it is reasonable to consider the thermal cycloelimination reaction as the rate-limiting step. Meanwhile, the starting materials, *N*-aryl succinamic acids, appear to be loaded more easily onto the solid-supported reagent.

The infrared (IR), ^{1}H NMR, and MS data of all the products are in good agreement with their structures. In addition, the melting points correspond to those of the literature[32] as well as the authentic samples prepared from the previously reported methods.

In conclusion, we have developed a new solid-phase synthesis protocol for the preparation of *N*-aryl succinimides. The main advantages of this process are the recyclability of the solid support and easy release of products from the linker as a concomitant of their formation. We anticipate the preliminary results are worthy of further investigation for the synthesis of other classes of heterocyclic compounds.

EXPERIMENTAL

Melting points were measured on an Electrothermal apparatus and are uncorrected. Chemicals were obtained from Merck (Darmstadt, Germany) and were used without further purification. The required *N*-aryl succinamic acid substrates **2a–g** were prepared near quantitatively from condensation between succinic anhydride and an equivalent amount of an aromatic amine in refluxing ethanol (95.5%) solutions.

Procedure for Preparation of Silica-Bound Benzoyl Chloride (SBBC)

$SOCl_2$ (25 mL) was added to 5.0 g of well-dried fine powders of silica gel 60 (0.063–0.200 mm) in a flask. The mixture was refluxed for about 3 h and then distilled to remove the excess $SOCl_2$. To 4.0 g of obtained white powders of silica chloride, a solution of 4-hydroxybenzoic acid (2.0 g) in CH_2Cl_2 (30 mL) and DMF (4 mL) was added and then refluxed for about 6 h. The suspension was filtered to separate the SBBA powders, and the precipitate was washed with 20 mL of 1:8 mixture of DMF/CH_2Cl_2 and dried at 100°C to give 5.62 g of SBBA. $SOCl_2$ (25 mL) was added to 5.0 g of SBBA and refluxed for about 3 h. The excess $SOCl_2$ was removed at reduced pressure, and the obtained white powder of SBBC (5.49 g) was stored in a dry bottle.

General Procedure for Preparation of Succinimides (4a–g)

SBBC (0.8 g) was added to a mixture of *N*-arylsuccinamic acid (1 mmol in each case of **2a–g**) in dry CH_2Cl_2. The mixture was refluxed according to the time mentioned in Table 2 and then was hot filtered. The filtered solids were washed with additional CH_2Cl_2 (20 mL). The combined solutions of CH_2Cl_2 were evaporated, and the residue was further purified by chromatography on silica gel using petroleum ether/ethyl acetate (2:1) as eluent to give the succinimides (**4a–g**). The residue of SBBC was renewed by washing it with 5 mL of dichloromethane, drying it in 60°C, and then refluxing it (3 h) in 8 mL of $SOCl_2$. The excess $SOCl_2$ was removed under reduced pressure.

Selected Data for Compound 4b

IR (KBr) $\upsilon_{max} = 3074$, 2984 (C-H); 1712, 1703 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) $\delta = 7.23$ (d, J 8.8 Hz, 2H); 7.03 (d, J 8.8 Hz, 2H); 3.87 (s, 3H); 2.92 (s, 4H) ppm. MS: m/z (%) = 204 (M^+, 100), 189 (3), 176 (6), 161 (10), 148 (9), 133 (10), 123 (19), 107 (11).

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