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PAPER

Direct Cycle between Coproduct and Reactant: an Approach to Improve Atom Economy and Applications for the Synthesis and Protection of Primary Amines

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Important goals of green chemistry include maximizing the efficiency of reactants and minimizing the production of waste. In this study, a novel approach to improve the atom economy of a chemical process was developed by incorporating a direct cycle between a coproduct and a reactant of the same reaction. To demonstrate this concept, recoverable 3,4-diphenylmaleic anhydride (**1**) was designed and used for the atom-economical synthesis of aliphatic primary amines from aqueous ammonia. In each individual cycle, only ammonia and alkyl halide were consumed, and **1** was recovered in nearly quantitative yield. In this approach for developing atom-economical protecting agents, **1** showed good performance as a recoverable protecting agent for primary amines. The broad substrate scope, good tolerance to various reaction conditions, and high reaction and recovery rates make **1** a valuable complement to conventional primary amine protecting agents.

Introduction

Atom economy is one of the fundamental principles of green chemistry.[1-7] Maximizing the efficiency of reactants and minimizing the production of waste are primary considerations for improving the atom economy of a reaction and are important goals of green chemistry.

Much progress has been achieved through the development of new chemical transformations that generate molecular complexity in a more atom-economical fashion, including novel catalysts, reaction media and tandem reactions.[8-11] However, many reactions still suffer from low atom economy because large amounts of waste or coproducts are generated simultaneously with the desired product. The development of new strategies to improve the atom economy of chemical processes is still in great demand.

Falling leaves returning to their roots provides a nice example of a “high atom economy” process that we can learn from nature. We were inspired to examine whether recovery the waste or coproduct from a reaction and using it as the reactant for the same reaction might be an approach to significantly improve the reaction’s atom economy. To the best of our knowledge, this approach of "direct cycle between coproduct and reactant" of the same reaction has not been reported.

The goal of this study was to create a general atom-economical method for the synthesis and protection of primary amines and to demonstrate our new approach for improving the atom economy of a chemical process. This is noteworthy given the potential applications of this approach in organic synthesis, where chemists must consider both green reactions and production methods.

Results and discussion

Application for the Synthesis of Primary Amines

Primary amines are important materials for both laboratory and industrial synthesis. In the preparation of primary amines *via* the Gabriel synthesis, the atom economy is generally poor as a stoichiometric quantity of phthalyl coproducts are generated along with the desired primary amines.[12-13] To circumvent long-standing problems that have limited the widespread application of the Gabriel synthesis, modifications of the original Gabriel synthesis, including the addition of catalysts, hydrazinolysis for the cleavage of the N-alkylphthalimide, and new Gabriel reagents have been reported.[14-18] It is necessary and important to improve the yields of every step within the Gabriel synthesis, including the alkylation of phthalimide and the hydrolysis of the resulting N-alkylphthalimide. In our opinion, however, an efficient recovery of the phthalyl coproducts after hydrolysis or hydrazinolysis and reapplying them in the same reaction is the key to an atom-economical Gabriel-type amine synthesis. Thus, the Gabriel synthesis was selected as the testing ground for demonstrating the potential of our approach.

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Technically, a novel Gabriel reagent is necessary to demonstrate the direct cycle between a coproduct and a reactant in a Gabriel amine synthesis. In our study, 3,4-diphenylmaleic anhydride (**1**) was designed and used in a cyclic synthetic procedure that included amidation, N-alkylation and hydrolysis (Figure 1). On a molecular level, **1** acts as a vise to secure NH_3 through covalent bonds (step a). After functionalization of the immobilized nitrogen atom (step b) and hydrolysis of the N-alkylated 3,4-diphenyl maleimides (step c), the liberation of the primary amine and recovery of **1** are achieved simultaneously. Except for the inorganic base and acid that are required for the N-alkylation and hydrolysis, only ammonia and alkyl halides are consumed in the construction of the primary amines, as **1** can thus be quantitatively recovered.

Although the synthesis of compounds **1**-**3** and their derivatives had been previously documented,[19-24] the development of reaction conditions with good to excellent yields for each step remained a challenge in our study. Compound **1** was obtained using 2-phenylacetic acid and 2-bromo-1-phenylethanone as the starting materials.[21] The conversion of **1** to 3,4-diphenylmaleimide (**2**) was studied under various reaction conditions (Table S1). It has been reported that 3,4-diarylmaleimides can be obtained from the corresponding anhydrides treated with methanolic ammonium bicarbonate, anhydrous ammonia, acetamide, or hexamethyldisilazane (HMDS).[19,22-24] To maximize the greenness and atom economy of the reaction, aqueous ammonia was first used as the nitrogen source and the reaction solvent. In addition, microwave irradiation was used to complete the reaction within several minutes. After examination of the influence of temperature, time and the amount of ammonia on yield, **2** was obtained in nearly quantitative yield under the optimized conditions: 2 eq. of ammonia and microwave irradiation at 120 °C for 4 min.

For the synthesis of 3,4-diphenyl N-alkyl maleimide (**3**) by N-deprotonation and N-alkylation of **2**, benzyl bromide was selected as the model alkylating reagent for optimizing the reaction conditions.[25-27] A "one-pot" method was first tested by using different single solvents as summarized in Table 1. The reaction in acetonitrile under microwave irradiation for 30 min led to a higher yield than in the other solvents (69% vs 34-45%, entries 1-4). However, a certain amount of benzyl alcohol was detected in the reaction mixtures. We hypothesized that a two-step procedure – N-deprotonation followed by N-alkylation under different conditions – would improve the final yield. To further improve the deprotonation yield of **2** in ethyl alcohol, ultrasound irradiation was employed and potassium hydroxide was used as the base. After ultrasound irradiation for 5 min, the residual solvent was evaporated and the resulting N-deprotonated **2** was alkylated in the presence of benzyl bromide in acetonitrile under microwave irradiation at 80 °C for 10 min. Thus, **3** was obtained in nearly quantitative yield through the N-deprotonation and N-alkylation of **2** under ultrasound and microwave irradiation conditions, respectively (Entry 9).

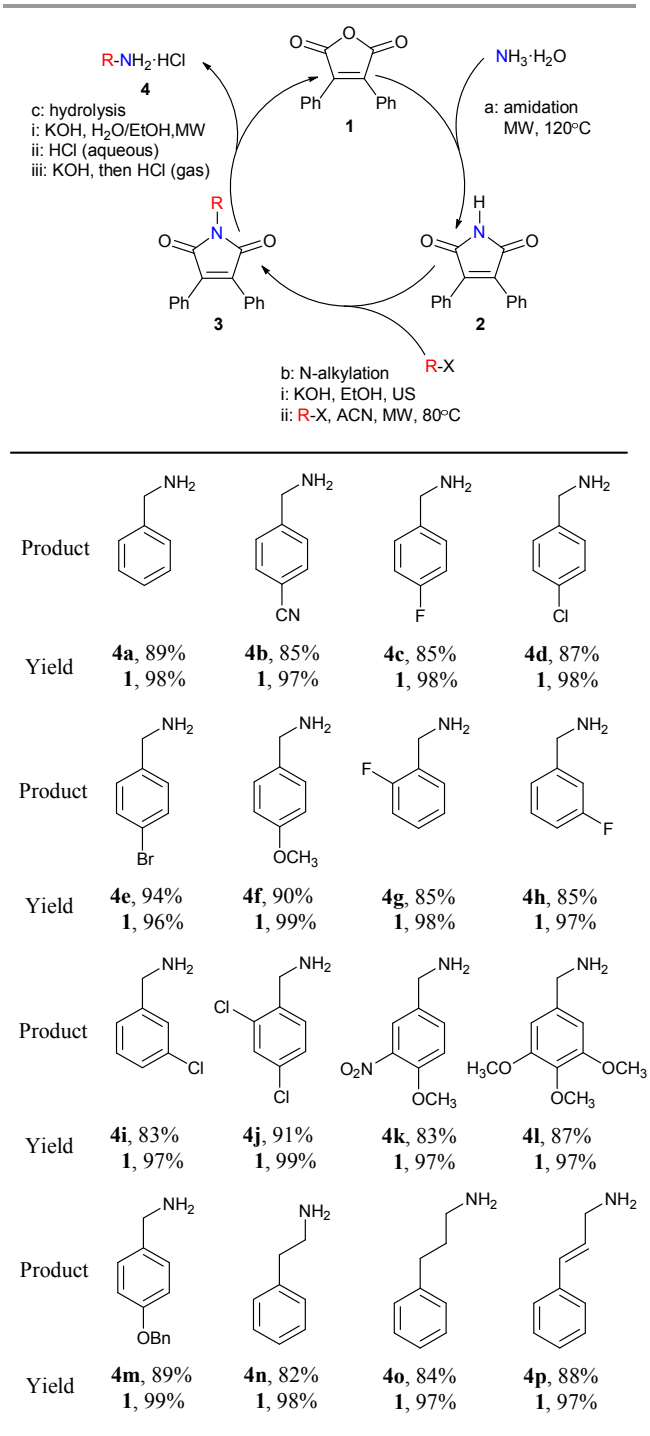


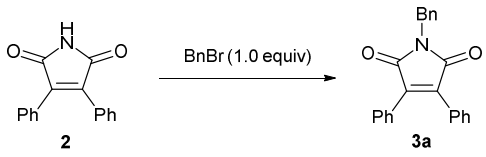
Figure 1 "Direct cycle between coproduct and reactant" approach for the synthesis of primary amines. All of the final primary amines were obtained in the form of hydrochlorides. The yields of **1** are the isolated recoveries after the three reaction steps in the cycle.

In our synthesis of primary amines, our main goals were a high yield of the target primary amines and a high recovery yield of **1** from the hydrolysis of **3**. Conventional methods for cleavage of the phthalimide in the Gabriel synthesis include using bases, acids, hydrazines and reductants.[18,28-30] In the preliminary

hydrolysis of **3**, 50 eq. of concentrated hydrochloric acid (6 M) was used in different solvent systems (Table S2). To our surprise, **3** was quite stable and remained unreacted, even after microwave irradiation at 100 °C for 30 min. Some literature[18,29,31] reports have indicated that 3,4-diarylmaleic anhydrides can be obtained from the corresponding 3,4-diaryl maleimides under basic conditions followed by acidification. Using a similar approach, 6 eq. of potassium hydroxide was used for the hydrolysis reaction in water/ethanol (2/1) with the assistance of microwave irradiation at 105 °C for 8 min. Notably, after the subsequent acidification by 18% hydrochloric acid, **1** precipitated from the reaction mixture and could be recovered in nearly quantitative yield by simple filtration. For the acidic aqueous layer, 50% potassium hydroxide was used to adjust the pH to approximately 11. After extraction and acidification using dry hydrogen chloride, benzylamine hydrochloride (**4**) precipitated and was obtained in 89% yield without column chromatography purification.

With the optimized conditions for the preparation of benzylamine in hand, application to the synthesis of other primary amines was successful. Subjecting various alkyl halides to the standard protocol afforded the desired aliphatic primary amines smoothly and in good yields (82-94%). Notably, in all of the examples, **1** was recovered in excellent yield after hydrolysis. In addition, a variety of functional groups, including halogen, hydroxyl and ether, were tolerated under the reaction conditions.

Table 1 Optimization of the N-alkylation step for primary amines synthesis



2 **3a**

Entry	Solvent	Base (eq.)	Temp[a] (°C)	Time[b] US+MW (min)	Yied (%)[c] **3a**
1	THF	K_2CO_3 (2)	80	0+30	34
2	Acetone	K_2CO_3 (2)	80	0+30	45
3	1,4-dioxane	K_2CO_3 (2)	80	0+30	39
4	CH_3CN	K_2CO_3 (2)	80	0+30	69
5	CH_3CN	K_2CO_3 (2)	80	10+20	78
6	CH_3CN	KOH (2)	80	10+20	85
7	EtOH+CH_3CN (1/1)	KOH (2)	80	10+20	93
8	EtOH+CH_3CN (1/1)	KOH (2)	80	5+10	92
9	EtOH+CH_3CN (1/1)	KOH (1.5)	80	5+10	92

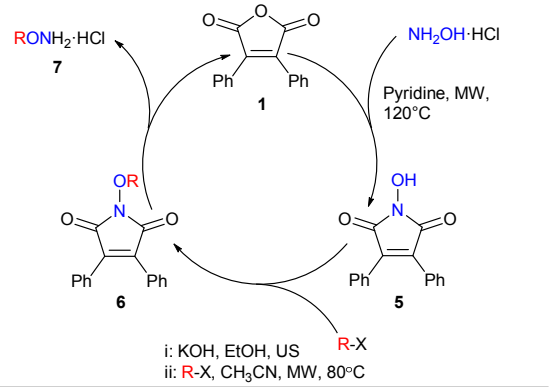
[a]Microwave irradiations were carried out in sealed reaction vessels under 80 °C. [b]Ultrasound irradiations were carried out under room temperature. [c]Isolated yield (%).

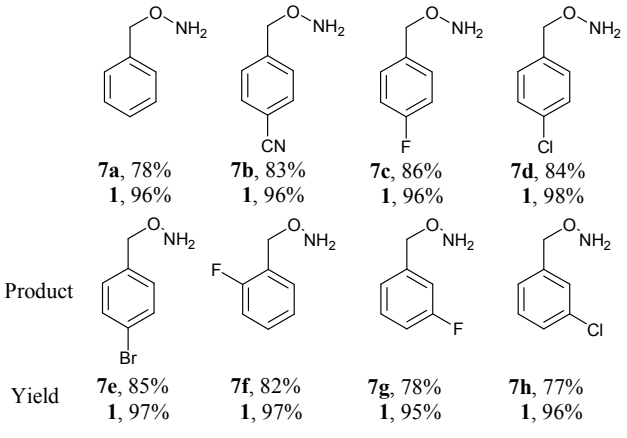
In the alkaline hydrolysis of N-alkylated phthalimides in the Gabriel synthesis, the ensuing acid treatment of the phthalate side product generally cannot lead to dehydration and ring-closing to generate a phthalic anhydride. Thus, the direct recovery of phthalates to improve the atom economy of Gabriel synthesis is difficult. In our study, base and ensuing acid treatment of **3** triggered the automatic ring-closing and precipitation of **1** from aqueous solution in nearly quantitative yield. We speculate that steric repulsion between the adjacent bulky phenyl rings and the high hydrophobicity of **3** and **1** play an important role in this automatic transformation.

Although a stoichiometric amount of **1** is needed in each individual cycle, it is clear that the amount of **1** remains almost unchanged at the end of a cycle. Thus, compound **1** allows for the direct cycle between a coproduct and a reactant of the same reaction. In our research, **1** showed over 95.9% purity (Figure S1) after recovery and was utilized for the reaction of further quantities of reactants. The unique chemical properties of **1** make it possible to synthesize primary amines with high atom economy.

Application for the Synthesis of O-alkylated Hydroxylamines

O-alkylated hydroxylamines are important materials that are used to synthesize O-substituted oximes and biologically active compounds containing an N–O linkage.[32,33] Encouraged by the above results, the synthetic route for primary amines was tested for the preparation of O-alkylated hydroxylamines, with slight modification. The cycle started with treatment of **1** with hydroxylamine hydrochloride in pyridine, followed by O-alkylation that was assisted by successive ultrasound and microwave irradiation, hydrolysis and acidification. By using various alkyl halides, the corresponding O-alkylated hydroxylamines were obtained in moderate to good yields (Figure 2). Furthermore, **1** was also recovered in close to quantitative yield after the cycle was completed.





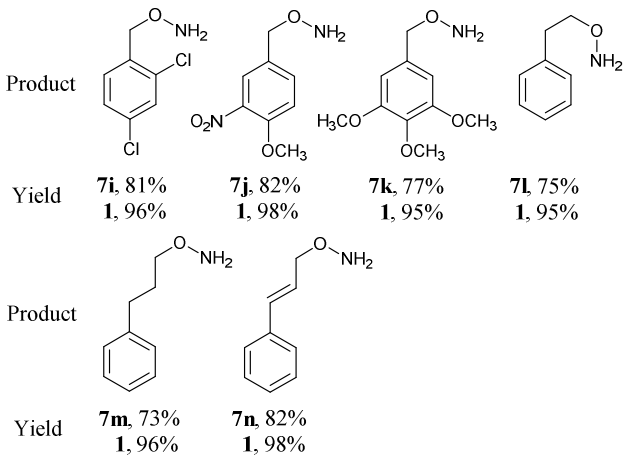
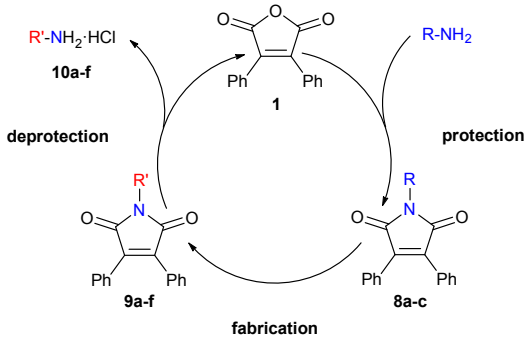


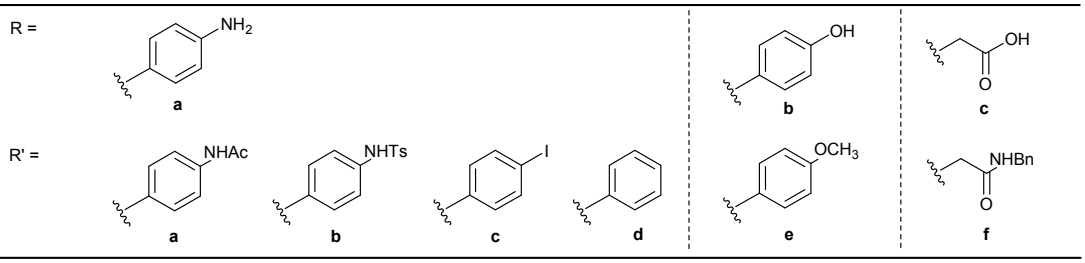
Figure 2 "Direct cycle between coproduct and reactant" approach for the synthesis of O-alkylated hydroxylamines. All of the final O-alkylated hydroxylamines were obtained in the form of hydrochlorides. The yields of **1** are the isolated recoveries after the three reaction steps in the cycle.

Application for the Protection of Primary Amines

Selective protection of amine groups is one of the most important aspects of organic chemistry. 1,2-Diphenylmaleyl (DPM) derivatives bear many similarities to the corresponding phthaloyl derivatives that have been used as protecting groups for amino functionalities. For example, **1** has been condensed with the amino group of carbohydrates and steroids, and removed by ethanolic hydrazine.[34] In addition, **1** has been used for the protection of glucosamine and its efficiency compared with other diacylamine protecting agents.[29,30] In these reported applications of DMP derivatives, however, relatively low protection/deprotection yields are important limitations, and the potential of using **1** as a recoverable amine protecting group was not fully studied.

To demonstrate our method for improving the atom economy of a chemical process that involves a protecting agent, **1** was used as a recoverable protecting agent in the modification of aliphatic and aromatic amine substrates (Figure 3). With *p*-phenylenediamine as the substrate, one of the amino groups could be selectively protected and the other modified by





Product	**8a**[i]				**8b**[i]	**8c**[ii]
Yield	93%				95%	85%
Product	**9a**[iii]	**9b**[iv]	**9c**[v]	**9d**[vi]	**9e**[vii]	**9f**[viii]
Yield	88%	65%	87%	66%	75%	90%
Product	**10a**[iii], **1**	**10b**[iv], **1**	**10c**[v], **1**	**10d**[vi], **1**	**10e**[vii], **1**	**10f**[viii], **1**
Yield	86%, 96%	97%, 94%	80%, 94%	80%,95%	98%, 96%	90%, 95%

Figure 3 "Direct circulation between coproduct and reactant" approach for the protection of primary amines. Compounds **10a-f** were obtained in the form of hydrochlorides. The yields of **1** were the isolated recovery rates of the hydrolysis steps. **Reagents and conditions:** (i) EtOH, 120 °C, MW, 10 min; (ii) Et_3N, EtOH, 120 °C, MW, 10 min; (iii) AcCl, EtONa, THF, 0 °C, 2 h; (iv) a) NaH, THF, RT, 0.5 h; b) TsCl, THF, 50 °C, 5 h; (v) a) $NaNO_2$, HCl, DMF, 0 °C, 20 min; b) KI, DMF, 50 °C, 0.5 h; (vi) $NaNO_2$, H_2SO_4, EtOH, 0 °C, 3 h; (vii) $(CH_3O)_2SO_2$, Na_2CO_3, acetone, RT, 3 h; (viii) benzylamine, DCC, HOBt, DMAP, THF, RT, 2 h; (ix) a) KOH, H_2O/EtOH: 2/1, 80 °C, 2 h; b) HCl (a.q.); c) HCl (dry); (x) a) K_2CO_3, H_2O/EtOH: 2/1, 60 °C, 2 h; b) HCl (a.q.); c) HCl (dry).

acetylation, sulfonylation, and diazotization followed by iodination and reduction. Deprotection of the amino groups was achieved by standard alkaline hydrolysis followed by acidification. In the case of 4-hydroxyaminobenzene, selective methylation of the hydroxyl group could be accomplished after protecting the amino group. **1** also showed good performance with the amino acid glycine in the protection/deprotection processes as well as tolerance for the coupling conditions. Compared with those obtained for traditional amine protecting agents, the yields and reaction rates under our conditions were significantly improved. Furthermore, **1** was recovered in good yield after deprotection and the atom economy of the chemical process was significantly improved.

Conclusions

The issue of phthalamide waste in the Gabriel synthesis was successfully solved by using recoverable **1** in this study. But the greenness of the synthesis was not entirely satisfactory owing to the use of organic solvents, inorganic base and acid to recover **1**. Thus, the greenness of the entire process needs to be further improved. However, the approach of a "direct cycle between coproduct and reactant" is an option for improving the atom economy of a chemical process, considering the reaction time, yields, and costs of both the materials and post-treatment processes.

In summary, a novel approach for improving the atom economy of a chemical process has been developed by incorporating the direct cycle between a coproduct and a reactant of the same reaction to reduce the production of waste. To demonstrate our approach, recoverable **1** was used for the atom-economical Gabriel-type synthesis of various aliphatic primary amines from aqueous ammonia. In each individual reaction cycle, only ammonia and alkyl halide were consumed, and **1** was recovered in nearly quantitative yield. Further application of **1** for the synthesis of O-alkylated hydroxylamines reactions featured a broad substrate scope and generally afforded the products in good to excellent yields. As part of our new approach, **1** showed good performance as a recoverable protecting agent for aliphatic and aromatic primary amines. The high protection/deprotection and recovery yields of **1** make it a valuable complement to conventional amine protecting reagents. Efforts including the application of **1** to the construction of other potentially valuable organic molecules and the immobilization of **1** on polymers for amine synthesis and protection are currently underway in our research group.

Acknowledgements

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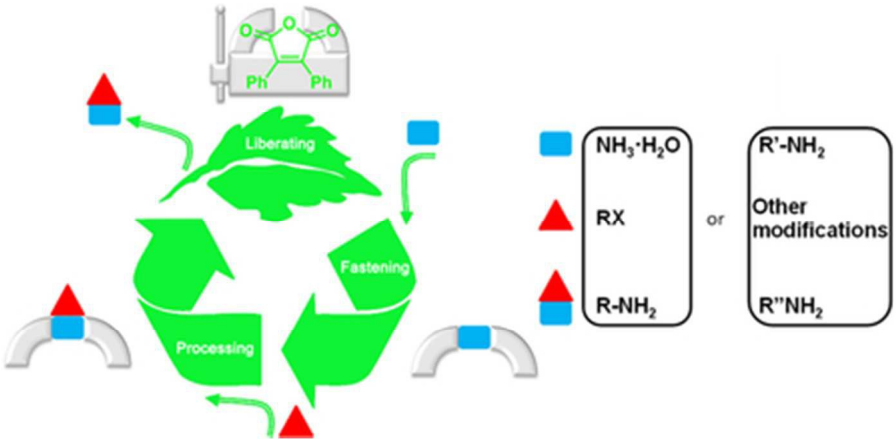

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