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Letter

Exploring Phthalimide as the Acid Component in the Passerini Reaction

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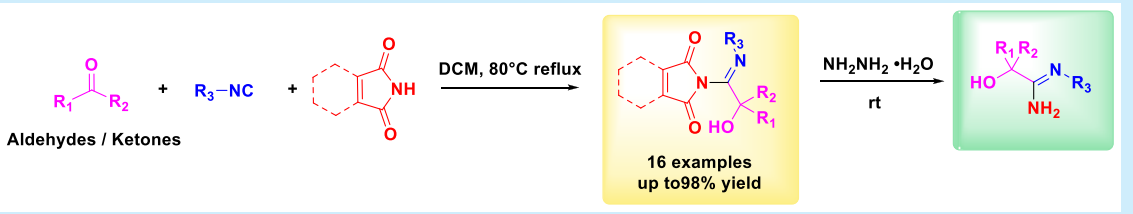

ABSTRACT: Multicomponent reactions, particularly the Passerini reaction, serve as efficient tools for the synthesis of druglike molecules and the creation of compound libraries. Despite the effectiveness of the Passerini reaction, the limited alternatives to the crucial carboxylic acid component pose a structural constraint. Here, we have discovered that the phthalimide moiety and its derivatives react in the Passerini reaction as an acid component. We explored their potential in synthesizing diverse and intricate molecules. The phthalimide moiety stands out as a favorable building block due to its oxidative stability, heat-stable characteristics, and resistance to solvents. Our approach introduces a novel perspective to multicomponent reactions by incorporating NH-based acid components, addressing the ongoing need for the development of innovative molecular scaffolds.

MCRs (multicomponent reactions) are chemical transformations that can efficiently generate a single multifunctional product by incorporating three or more reactants with almost all their atoms and are thus regarded as a considerable toolbox to expand molecular diversity and complexity in synthetic and medicinal chemistry.[1−3] Among them, the Passerini (Figure 1a)[4] and Ugi (Figure 1b)[5] MCRs have experienced rapid growth with applications in diverse areas of fundamental and applied chemistry, because of the ready access of a large number of starting materials. Both reactions share a similar mechanism, which begins with the activation of the aldehyde or imine by the carboxylic acid component. However, the utilization of carboxylic acids could also be considered as a limitation of the reactions due to a finite number of readily available variations. Besides carboxylic acids, very few alternative acids were described[6,7]

El Kaim et al. reported some notable examples by using O-arylative compounds as a replacement of carboxylic acids in both Passerini and Ugi reactions to access α-aryloxy-amides,[8] as well as O- and N-arylamides[9] (Figure 1c). Subsequently, the use of other starting materials instead of carboxylic acids has been reported (Figure 1A). A direct alkylative Passerini reaction was reported using free aliphatic alcohols to obtain the corresponding α-alkoxyl amide products (Figure 1d).[10] The requirement for α,β-unsaturated aldehydes and *tert*-butyl isocyanide, in addition to the use of an In catalyst, limited the application of this methodology. Later on, O-silylative[11] (Figure 1e) and O-phosphinative[12] (Figure 1f) Passerini reactions were developed for the synthesis of α-siloxyamides and α-(phosphinyloxy)amides by replacing the carboxylic acid with triphenylsilanol and phenylphosphinic acid, respectively. Our group also reported N-hydroxamic acids as acid components in Passerini reaction toward α-aminoxy-amides (Figure 1g).[13] Moreover, we published a highly improved version of the lesser-used Passerini tetrazole reaction using $TMSN_3$ in water/methanol and ultrasound.[14] In 2018, Saya et al. reported the use of hexafluoroisopropanol as an acid component in the Passerini reaction, synthesizing β-amino alcohols via a two-step one-pot approach (Figure 1h).[15] To date, most carboxylic acid replacements in the Passerini reaction are OH-based acid bioisosteres. Thus, the discovery of non−OH-based acid components in the Passerini reaction is underexamined and of great interest.

Phthalimide, which is a bicyclic aromatic nitrogen heterocycle, has a pK_a value of 8.3 and can be considered as a carboxylic acid bioisostere. However, due to its lipophilic and neutral properties, phthalimide and its derivatives can easily cross biological membranes and therefore exhibits pharmaceutical potential.[16] A large number of phthalimide subunits containing compounds has been designed and developed as antitumor,[17−19] anti-inflammatory,[20,21] anti-Alzheimer (AD),[22]

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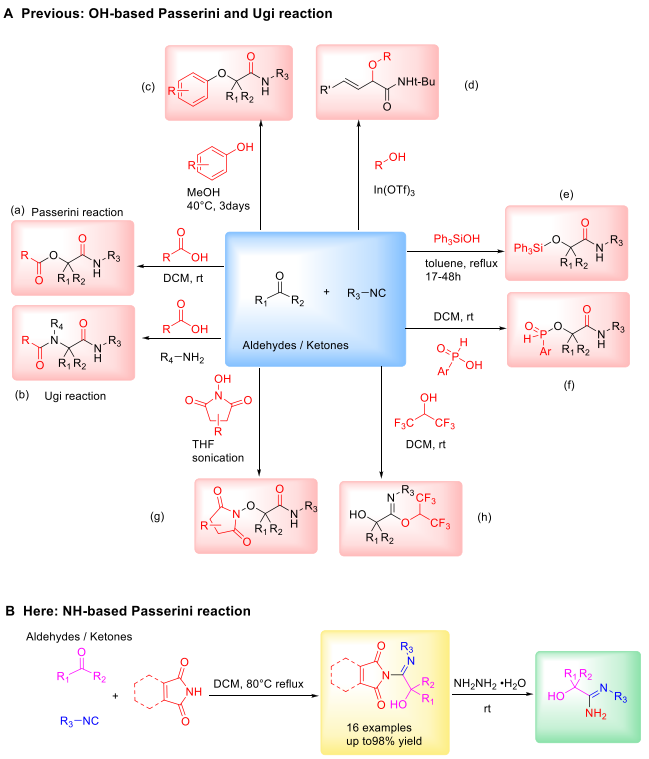


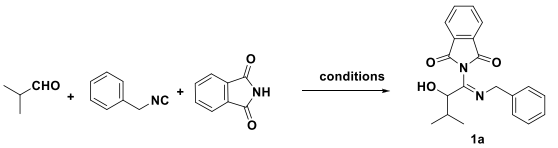
Figure 1. Different acid components in the Passerini reaction.

antipsychotic,[23] antimicrobial,[24] anticonvulsant,[25] anxiolytic,[26] and anti-HIV agents.[27] Several of these compounds have reached the market for the treatment of multiple myeloma (Lenalidomide),[28] psoriasis (Apremilast),[29] rheumatoid arthritis, and shock septic syndrome (LASSBio-468).[30] In addition to its abundant medicinal applications, the phthalimide moiety also plays an important role in synthetic chemistry and is considered as a precursor for the synthesis of amines[31] and anthranilic acids.[32]

On the other hand, the acidic properties of phthalimide remain less explored. We hypothesized that the phthalimide moiety could be introduced in MCR scaffolds to form multisubstituted compounds, and, here, we explore the potential of phthalimide as the acid component in the Passerini reaction.[33]

To develop our strategy, we performed optimization of the reaction conditions. For this, isobutyraldehyde (1.0 equiv), benzyl isocyanide (1.0 equiv), and phthalimide (1.0 equiv) were utilized as starting materials (Table 1). Aprotic solvents are more preferable than protic solvents in Passerini-type reactions, and among them, DCM is the most commonly used solvent.[34] Therefore, we started the investigation by using DCM at room temperature. However, phthalimide has poor solubility in DCM and the starting materials did not fully convert, even after 2 days of reaction, resulting in only 20% yield (Table 1, entry 1). Thus, the solubility of phthalimide is significantly hindering the reaction. We hypothesized that, by increasing the temperature of the reaction, the solubility of phthalimide could improve and, as a consequence, the reaction would be faster. Indeed, by performing the reaction at 55 °C, the yield increased to 43% (Table 1, entry 2). Moreover, the investigation of different solvents could also be a factor that could further improve the reaction. Although THF and MeOH improved the solubility of phthalimide, the yields decreased

Table 1. Optimization of Reaction Conditions



entry	solvent	time (h)	base	temperature (°C)	yield[a] (%)
1	DCM	48	–	rt	20
2	DCM	12	–	55	43
3	THF	12	–	55	40
4	DCM:THF(1:1)	12	–	55	35
5	MeOH	12	–	55	trace
6	DCM	12	Et_3N	55	ND
7	THF	12	Et_3N	55	ND
8	DCM:DMF(9:1)	12	Et_3N	55	ND
9	dioxane	12	Et_3N	55	ND
10	DCM	4	–	80	90
11	THF	4	–	80	52
12	DCM:DMF(1:1)	4	–	80	81
13	DCM:DMF(9:1)	4	–	80	83
14	dioxane	4	–	80	77

[a]Isolated yields.

(Table 1, entries 3–5). Furthermore, the use of organic bases could form ions with the phthalimide, due to its acidic properties, and possibly help it dissolve in the organic solvents as well. However, the addition of trimethylamine failed to boost the reaction and, on the contrary, hindered the formation of product (Table 1, entries 6–9). Thus, after all the attempts, we concluded that the major factor to improve the yield of the reaction is the temperature. We returned to our initial reaction conditions and increased the temperature to 80 °C. To our delight, the increased temperature not only provided excellent yields, but also accelerated the reaction time to 4 h (Table 1, entries 10–14). Next, we tested different solvent systems with the aim of improving the solubility of phthalimide. Reactions in THF and dioxane led to lower yields (52% and 77%, respectively; see Table 1, entries 11 and 14). The use of solvent mixtures (DCM and DMF) led to good yields of 81% and 83% (Table 1, entries 12 and 13); however, pure DCM as solvent provided the best yield of 90% (Table 1, entry 10).

With these optimized conditions in hand, we studied the substrate scope, using diverse oxocomponents and isocyanides that were conveniently synthesized according to our recently published procedure.[35] Initially, we used various aliphatic and aromatic isocyanides (Scheme 1). Most of the aromatic isocyanide components resulted in good to excellent yields from 74% to 99% (**1a**–**1h**). Monosubstituted aromatic isocyanides (*p*-chloro, *p*-methoxy) led to better yields of 80% and 99%, respectively, compared to nonsubstituted aromatic isocyanides (**1a**, **1b**). Additionally, 2-(2-phenyl-1*H*-indole-3-yl)ethyl isocyanide (**1d**) with a 1*H*-indole substitution led to a good yield of 78% as well. As an aliphatic isocyanide, cyclohexyl isocyanide was utilized in this reaction and resulted in a good yield, 91%. However, tert-butyl isocyanide and tert-octyl isocyanide did not give us any corresponding products. In contrast to the aromatic isocyanides, the outcome for aliphatic isocyanides depends on their substitutions.

Next, we turned our focus to the aldehyde component. We observed that aromatic aldehydes decreased the reaction yield

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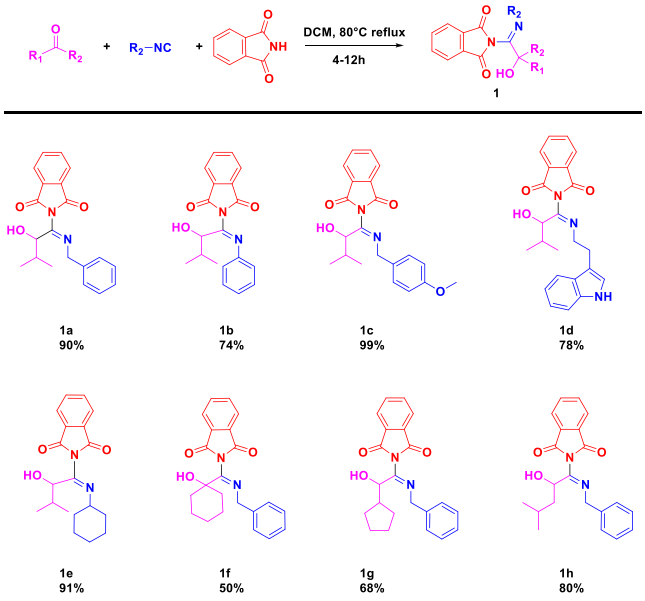
Scheme 1. Substrate Scope of the Phthalimide Conducted Passerini Products (1)[a]



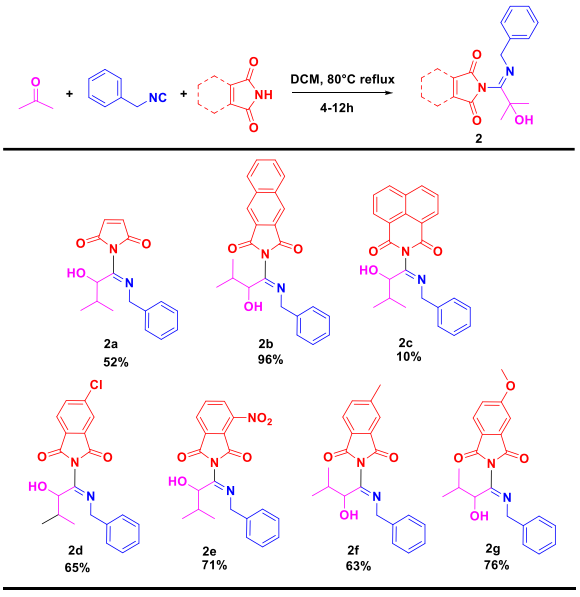
[a]Isolated yield.

and only gave trace amounts of product, whereas both the linear and cyclic aliphatic aldehydes displayed moderate to good yields (80% (**1g**) and 68% (**1h**), respectively). Noteworthy, an example with a ketone was also successful, resulting in a 50% yield (**1f**). The comprehensive incorporation of different oxo and isocyanide components resulted in the creation of a compound library characterized by high complexity and diversity. This approach unveiled the notable building block availability and good functional group tolerance of the current strategy.

Besides the use of phthalimide, we envisioned that N-formylformamide-containing conjugated cyclic compounds, with low pK_a values, could be treated as acid isosteres and used in the present strategy as well (Scheme 2). The exploration started with 1*H*-pyrrole-2,5-dione (**2a**), which lacks one phenyl ring, compared with phthalimde. The lack of one phenyl ring reduced the acidic properties and led to a decreased yield of 52%, probably due to its less acidic character. On the other hand, addition of phenyl rings on different positions resulted in diverse yields. 1*H*-Benz[f]-isoindole-1,3(2*H*)-dione (**2b**), which retained the basic 5-membered *N*-formylformamide cyclic scaffold of phthalimide, reacted with high yield (96%), whereas 1*H*-benzo[de]-isoquinoline-1,3(2*H*)-dione (**2c**), containing a 6-membered *N*-formylformamide cyclic scaffold, resulted in only 10% yield. Furthermore, the effect of diverse substitutions was explored as well. Substituents on positions 4 and 5, including halogens (**2d**), nitro (**2e**), methyl (**2f**) and methoxyl (**2g**) substituents were well tolerated with moderate to good yields. In summary, the successful strategy using phthalimide and derivatives with different substituents in the Passerini reaction resulted in a diverse library of products.

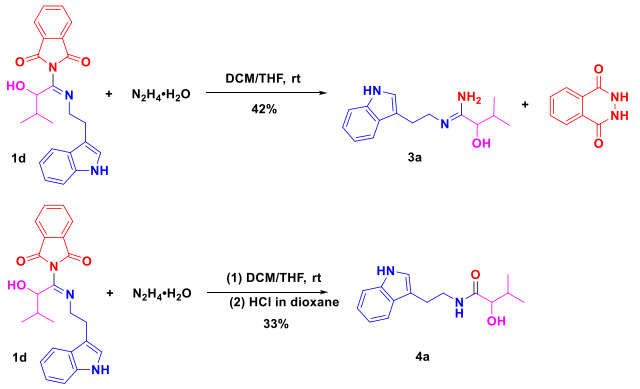
As an application of this new reaction, we next investigated the cleavage of phthalimide toward the amidine alcohols, which are important intermediates for the synthesis of bioactive heterocycles[36,37] (Scheme 3). We first conducted

Scheme 2. Substrate Scope of Phthalimide Derivatives (2)[a]



[a]Isolated yield.

Scheme 3. Cleavage of Phthalimide for the Synthesis of α-Amidine Alcohol (3)[a]



[a]Isolated yield.

the Passerine reaction in 1 mL of DCM to the formation of 2-(1-((2-(1H-indol-3-yl)ethyl)imino)-2-hydroxy-3-methylbutyl)-isoindoline-1,3-dione (**1d**). The reaction was monitored by TLC and upon completion, 1 mL THF was added to the reaction mixture, followed by hydrazine. The reaction mixture was stirred for 1 h at room temperature, forming the amidine (**3a**). However, when HCl in dioxane was added to the reaction mixture, the expected HCl salt was not observed, and unexpectedly, amide (**4a**) was formed by hydrolysis. All of these reactions were conducted in a one-pot manner, without column chromatography of the intermediates (Scheme 3).

Based on the generally accepted Passerini reaction mechanism, we propose a similar mechanism (Scheme 4). Herein, the activation of the aldehyde by the acidic NH moiety of phthalimide increases the carbonyl electrophilicity, followed by the nucleophilic attack of the isocyanide to the carbonyl group of the aldehyde. Subsequently, the phtalimide −N reacts with the isocyanide carbon including the formation of a cyclic intermediate **A**. The hydrogen of phthalimide rearranges to the aldehyde oxygen and gives the corresponding alcohol.

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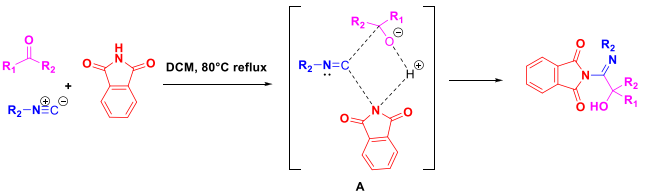
Scheme 4. Predicted Mechanism of the Passerini Reaction



In summary, we have demonstrated an unprecedented utilization of the phthalimide moiety, serving as a substitute for the carboxylic acid component in the Passerini reaction. The methodology underwent scrutiny through a small library synthesis, showcasing a robust tolerance for both aromatic and aliphatic building blocks. The flexibility of achieving product diversity across all components was evident. The subsequent cleavage of the phthalimide facilitated the straightforward synthesis of α-amidine alcohols and α-amide alcohols, compounds typically challenging to access.[38] Noteworthy, α-amidine alcohols are a class of compounds rarely found in organic chemistry, with an interesting hydrogen bonding pharmacophore, and are highly under-represented in medicinal chemistry.[39] Our novel synthetic approach exhibits significant potential for applications in the screening library enrichment. Ongoing efforts in our laboratory are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03962.

Experimental procedures, compound data, NMR spectra, HRMS, and crystal structure determinations (PDF)

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Notes

The authors declare no competing financial interest.

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