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Petasis three-component reaction accelerated by trifluoroacetic acid: synthesis of-indoline derived glycines

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R_3 can be electronic donating or withdrawing groups

Isolated yields range from 65% to 94%

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Petasis Reaction

Boronic acid

Indoline

Glycine

trifluoroacetic acid

ABSTRACT

We have discovered that trifluoroacetic acid is an efficient catalyst to accelerate the Petasis three-component, one-pot process, reducing reaction times, and offering good to excellent yields. A series of azaarene-derived glycines have been successfully achieved via the TFA-accelerated Petasis reaction. To our best knowledge, the use of TFA to accelerate Petasis reaction has not been reported in the literature. By virtue of the operational simplicity, the present TFA-catalyzed Petasis reaction, capable of shortening reaction times, might find applications in other instances of the widely used Petasis reaction.

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1. Introduction

Multicomponent reactions (MCRs) are highly efficient chemical transformation. They are atom and step economical transformations. MCRs can provide the construction of an arrays of organic compound libraries of diverse structures in medicinal chemistry field. Many efforts have been devoted to investigate new types of the multicomponent strategic pathway due to their importance in the synthesis of complex molecules in the pharmaceutical area. Among many reported MCRs, the three-component one-pot Petasis reaction involves boronic acid in the Mannich-type condensation reaction. Petasis reaction is quite remarkable because the boronic acid is inert toward aldehyde functionality though it reacts efficiently with the double bond of an imine or an iminium. By virtue of this exquisite reactivity, Petasis reaction has become highly attractive because this three-component, one-pot Petasis reaction allows to prepare an assortment of interesting compounds among which amino-acids, heterocyclic compounds and alkylaminophenols are the most easily accessible.

During the course of our discovery program directed to the preparation of histone deacetylase enzyme inhibitors [HDACi] comprising both 2-(indolin-1-yl)-2-arylmethyl and hydroxamic acid moieties as shown in **Figure 1**, potential chemotherapeutic agents against the proliferation of human cancer cells, we required precursors such as 2-(nitroindolin-1-yl)-2-arylacetic acids, as depicted in **Figure 2**, in order to prepare a series of the aforementioned target compounds for our discovery program.

Figure 2

We chose Petasis reaction to prepare the precursors because it allowed in one step to build all parts of our desired precursors as depicted in **Figure 2**. Petasis reaction of three-component, one-pot synthesis has been received intense attention in medicinal and combinatorial chemistry.¹⁻¹¹ Petasis synthesis can provide α -arylglycines, non-proteinogenic aminoacids. It offers many attractive features to the medicinal chemistry including facile entries to a large number of α -arylglycines of new and diverse structures with high atom and step economy. We became interested in the possibility of applying Petasis reaction to the preparation of our targeted precursors of α -amino acids ideally suited to a variety of substituent R_3 . While Petasis reaction is

operationally simple and convenient, the reaction suffers, however, from low reaction reactivity. It requires, in general, long reaction time, ranging from several hours to several days. In spite of the simplicity of this one-pot reaction, the long reaction time renders the reaction unamenable for speedy preparation.

New strategies have been developed in order to enhance the reactivity of Petasis reaction in order to shorten the reaction time. Methods include the use of water¹², protic solvents, aprotic solvents¹³, ionic liquid, organotrifluoroborates, thioureas, solvent-free¹⁴ and the use of higher reaction temperatures. Those strategies brought about moderate improvement of the reactivity.

Many Petasis reactions still need 12 hours or longer to complete at ambient temperature.

Different solvents have been attempted to improve the reactivity. While dichloromethane slightly enhanced the reactivity, the reaction time is still long. Nanda et al. have conducted a study of the reactivity in protic solvents, and discovered that the use of hexafluoroisopropanol (HFIP) as an additive in dichloromethane could promote the reactivity.¹⁵⁻¹⁸ Indeed, they found that by adding 10 vol % of hexafluoroisopropanol in dichloromethane dramatically accelerated the reaction. They compared the reactivity of Petasis reaction conducted in dichloromethane with 10 vol % of hexafluoroisopropanol as an additive to the reactivity of the same reaction conducted in dichloromethane alone. They discovered that they were able to reduce the reaction time of Petasis reactions conducted in CH₂Cl₂ alone from more than twenty hours to few hours by using 10 vol % of hexafluoroisopropanol as an additive.

2. Results and Discussion

In the course of our work aimed at the preparation of the targeted precursors: 2-(nitroindolin-1-yl)-2-arylacetic acids (**Figure 2**), we had reason to search for new avenues to enhance the reactivity of Petasis reaction. We have now found that the use of a catalytic amount of trifluoroacetic acid in dichloromethane (1:30, v/v) in the preparation of 2-(4-methylphenyl)-2-(5-nitroindolin-1-yl)acetic (**Figure 2** wherein R₃ = 4-CF₃) had driven the reaction to completion in two hours (79% isolated yield on 95% conversion) while the same reaction, conducted in a mixed solvent of 10 vol % of hexafluoroisopropanol in dichloromethane required 7 hours to complete, and the yield was lower (60% isolated yield on 76% conversion).

Table 1. Reactivity enhanced by trifluoroacetic acid (TFA) versus that by hexafluoroisopropanol (HFIP)

Entry	R ³ in Bronic acid	Product : 4	Time (h)	% of Conversion ^[a]	
				TFA	HFIP
1	4-CF ₃	4-1	1.5	95	76

2	3,5-di-CF ₃	4-2	1	88	91
3	4-CO ₂ CH ₃	4-3	1	89	76
4	4-CH ₃	4-4	1.5	86	93
5	2-CH ₃	4-5	2	79	90

^aDetermined by HPLC

The success of the use of a catalytic amount of TFA to accelerate this Petasis reaction of 5-nitroindoline prompted us to examine the generality of this reactivity enhancement. We decided to compare few examples of the reactions catalyzed by TFA (condition A) to the same reactions carried out in the mixed solvents of 10 vol % of hexafluoroisopropanol in dichloromethane (condition B). We compared the progress of the reaction by determining the amount of the products formed at the early stage of the reactions carried out under condition A, and in condition B by means of HPLC analysis.

As shown by the data in **Table 1**, both reactions using either a catalytic amount of TFA in CH₂Cl₂ (condition A) or using hexafluoroisopropanol (HFIP) at 10 vol % in CH₂Cl₂ (condition B) offered approximately the same amount of the desired product after 1 ½ h to 2 h reaction times. These findings indicated that the acceleration of Petasis reaction achieved by a catalytic amount of TFA in CH₂Cl₂, (condition A) is as efficient as the same reaction carried out using 10 vol % of hexafluoroisopropanol in dichloromethane (condition B). The acceleration of Petasis reaction achieved by catalytic TFA in CH₂Cl₂, developed above should be applicable to other boronic acids with different substituents: activating and deactivating groups. We decided to synthesize a number of examples to illustrate the general utility of this TFA accelerated Petasis reaction. The examples are depicted in **Table 2**.

Table 2. Reactions of 5-nitroindoline with a variety of boronic acids catalyzed by trifluoroacetic acid (TFA)

Entry	R ³ in Bronic acid	Product: 4	Time (h)	Isolated yields (%)
1	4-CH ₃	4-4	4	83

2	2-CH ₃	4 - 5	4	65	14	4-Cl	4 - 17	7	65
3	4-C ₂ H ₅	4 - 6	5	86	15	4-Br	4 - 18	5	69
4	4-isoC ₃ H ₇	4 - 7	5	65	16	3,5-di-Br	4 - 19	6	84
5	3-CH ₃	4 - 8	4	67	17	4-CO ₂ CH ₃	4 - 3	5	65
6	3,5-di-CH ₃	4 - 9	3	65	18	4-CF ₃	4 - 1	2	79
7	4-OCH ₃	4 - 10	3	79	19	3,5-di-CF ₃	4 - 2	2	78
8	3-OCH ₃	4 - 11	2	65	20	4-CH ₂ Br	4 - 20	4	79
9	2,5-di-OCH ₃	4 - 12	6	81	21	4-CH ₂ Ph	4 - 21	6	94
10	3,4,5-tri-OCH ₃	4 - 13	3	81	22	4-NO ₂	4 - 22	16	No reaction
11	3,4-(1,4-dioxan-2,3-diyl)-	4 - 14	4	65	<p>Indoline derived arylglycines via Petasis reaction with glyoxylic acid, 5-nitroindoline and substituted boronic acid have been successfully prepared. The scope of the reaction with regard to the component of the substituted boronic acids was explored. To our best knowledge, using trifluoroacetic acid to accelerate Petasis reaction has not been reported in the literature. Several important generalizations emerge from the data in Table 2. First, all the trifluoroacetic acid-catalyzed Petasis reactions (Except: entry 22) completed (based on HPLC) within few hours at room temperature offering good to excellent yields (isolated yields). The results indicated that trifluoroacetic acid provided a beneficial effect in accelerating Petasis reaction. In fact, such accelerated reactions offered acceptable yields and achieved with reasonable reaction times. Second, both activating groups or deactivating groups in the phenyl ring of boronic acids worked well in this three-component reaction (examples: entry 7 versus entry 18). The reaction with two deactivating groups: CF₃ in the phenylboronic acid offered 78% yield in 2 hours at room</p>				
12	4-SCH ₃	4 - 15	1	84					
13	H	4 - 16	2	70					

temperature [Entry 19]. However, when the phenyl boronic acid had a very strong electron-deficient group such as 4-nitrophenylboronic acid, the reaction met with failure [Entry 22]. Third, when the reactions were carried out under TFA catalytic conditions, the sterically hindered phenylboronic acids did not pose any problem. In fact, the boronic acids with ortho-substituted group provided good yields with acceptable reaction times [Entries 2 and 9]. Finally, TFA is not only an inexpensive material, but also employed only in an amount of 0.005 mol % as compared to the method using out using 10 vol % of hexafluoroisopropanol in dichloromethane (condition B).

3. Conclusion

We found that TFA is an effective catalyst to accelerate Petasis reaction to prepare indoline derived arylglycines starting with glyoxylic acid, 5-nitroindoline and substituted boronic acid. A series of azaarene-derived glycines have been successfully achieved via this newly found accelerated Petasis reaction. To our best knowledge, the use of TFA to accelerate Petasis reaction has not been reported in the literature. By virtue of the operational simplicity, the present method might find applications in other areas of the widely used Petasis three-component reaction.

4. General Procedure for TFA accelerated Petasis' three-component reaction

We described the synthesis of the compound 1 (Table 2) to illustrate the general procedure for TFA accelerated Petasis three-component reaction. The descriptions of the preparations of all reported compounds are in supporting information section.

To a magnetically stirred mixture of 5-nitroindoline (0.164g, 1.0 mmol), 4-tolylboronic acid (0.135g, 1.0 mmol) and glyoxylic acid monohydrate (0.092g, 1.0 mmol) in CH_2Cl_2 (5ml) was added TFA (20 μl). The mixture was stirred at room temperature for 4 hours. After the completion of the reaction (TLC monitoring), half of the solvent was evaporated by means of a rotovap. The resulting solid was filtered through a sintered glass funnel. The collected solid was thoroughly washed with petroleum ether and a small amount of ice water (5ml), and then dried in vacuo at room temperature for 24 h to afford 0.26g (83.3%) of 2-(5-nitroindolin-1-yl)-2-(p-tolyl) acetic acid as a light yellow solid. Mp: 177.0-178.1 $^{\circ}\text{C}$. ^1H NMR(400MHz, $\text{DMSO}-d_6$): δ =8.00(1H, m), 7.86(1H, s), 7.26(4H, m), 6.70(1H, d, J =8.94Hz), 5.71(1H, s), 3.81(1H, m), 3.21(1H, m), 3.00(2H, m), 2.32(3H, s); ^{13}C NMR (400MHz, $\text{DMSO}-d_6$): δ =171.16, 156.59, 137.70, 137.38, 131.42, 130.49, 129.23, 128.83, 126.02, 120.28, 104.61, 61.16, 49.18, 26.15, 20.68 ppm. Calculated for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$, MS (ESI): m/z =313.1181 ($\text{M}+\text{H}$) $^{+}$.

Acknowledgments

Financial support from National Science Foundation of China [Grant No. 21176018] is gratefully acknowledged.

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