Utilization of Solid Acid SO_4^{2-}/TiO_2 as Catalyst to the Three-Component Mannich Reaction at Ambient Temperature

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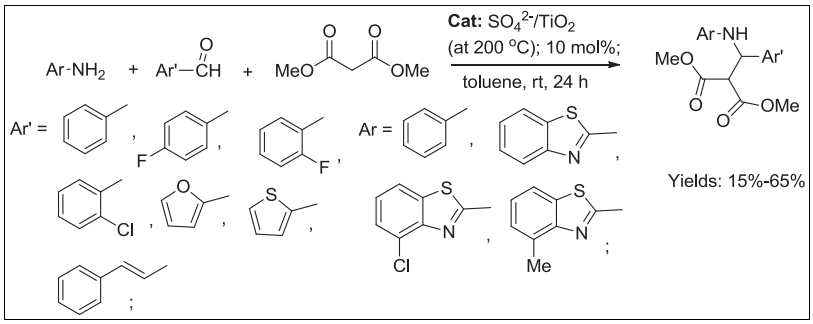

The three-component Mannich reaction of among dimethyl malonate, aromatic primary amine, and aromatic aldehyde was made successfully in the presence of solid acidic catalyst SO_4^{2-}/TiO_2, with excellent catalytic activity, as compared to SO_4^{2-}/γ-Al_2O_3 and SO_4^{2-}/ZnO. To the best of our knowledge, SO_4^{2-}/TiO_2 prepared at varied calcination temperatures can perform different intensities of Lewis and Brønsted acidities. Because of this point, under the optimum conditions, the effect of SO_4^{2-}/TiO_2 (prepared at 200°C) was much more than that of SO_4^{2-}/TiO_2 (prepared at 300°C or 400°C) in the three-component Mannich reaction. In observing ionization activation mode of the three-component Mannich reaction, it disclosed that the plausible mechanism possibly undergoes formation of aldimines and transformation of aldimines into β-amino esters by applying solid acidic catalyst SO_4^{2-}/M_xO_y.

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INTRODUCTION

Suitably substituted amino esters and their derivatives are considered as potent building blocks for designing various pharmaceutical or medicinal products and their intermediates [1,2]. In particular, certain optically active β-amino esters with appropriate configuration of the chiral center have been widely applied to generate products of biological significance such as peptide mimics, antibiotics, herbicides, pharmacological agents, enzyme inhibitors, and catalytic antibodies [3–6]. The prospective β-amino ester derivatives which are usually characterized by the presence of a chiral carbon center are conventionally synthesized by Mannich or Mannich-type reaction of pregenerated or *in situ* electrophilic aldimines (EI) with malonate esters serving as the nucleophile (Nu). Numerous synthetic approaches to diverse amino ester derivatives (both racemic and chiral) have been investigated and documented in the last 10 years [7–22].

Regarding mechanism of acid-catalyzed Mannich or Mannich-type reactions, both non-covalent hydrogen-bond activation of the imine with Brønsted Lewis acids as well as ionic activation involving the formation of an ion pair from the interaction of lone pair of electrons of nitrogen atom with acidic proton may be envisaged. These catalytic interactions with the electrophilic substrate are presumably responsible for lowering the activation energy of the overall reaction thereby promoting the formation of the Mannich adduct favorably. Although the activation of substrates in various Mannich-type reactions via non-covalent hydrogen-bond interaction has been widely exploited [23–28], the corresponding activation of imines through ion-pair formation has been scarcely reported. It appears that Mannich reactions catalyzed by relatively stronger Brønsted Lewis acids facilitate the nucleophilic attack of enolizable carbonyls like malonate to pi-antibonding orbital of an sp^2-hybridized carbon center of electrophilic aldimine [29–33]. In the absence of a base initiator, the substrate under this reaction condition presumably undergoes activation through an ionic mechanism involving the generation of an ion-pair.

Solid acids derived from SO_4^{2-}/M_xO_y have been regarded as highly efficient and environment-friendly catalysts for various organic transformations such as isomerization and alkylation reactions. These acids which are usually associated with two catalytic sites are able to activate a wide range of substrates because of the presence of both Brønsted and Lewis acidic sites**.** In this

regard, Jing and co-workers [34] had made an interesting observation that solid acid SO_4^{2-}/TiO_2 prepared at various calcination temperatures exhibited Lewis and Brønsted acidities to different extents, as confirmed from their *in situ* FIIR-pyridine absorption frequencies at 1450 cm^{-1} and 1540 cm^{-1} respectively. It appears that ionic mode of mechanism is greatly assisted by the presence of a water source which can readily convert Lewis acidic sites into active Brønsted acids to activate the aldimines through ion-pair formation in a typical Mannich reaction, as depicted in Figure 1.

Furthermore, this acid catalyst can help to initiate the Mannich reaction not only through chemical interaction but also by offering large surface area to the reacting components. In continuation to our synthesis of Mannich adducts [35–38], herein, we report synthesis of β-amino esters through Mannich-type reaction of aromatic aldimines with dimethyl malonate catalyzed by acid catalyst SO_4^{2-}/M_xO_y. Under optimal conditions, in order to account for the observed products, an ionic mechanism of catalytic activation of the aldimines has been proposed.

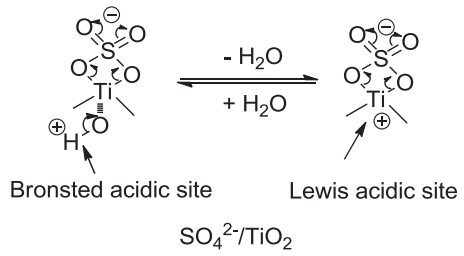


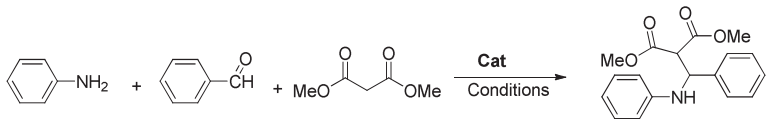
Figure 1. Plausible conversion of Lewis acid to Brønsted acid in SO_4^{2-}/TiO_2 system.

RESULT AND DISCUSSION

As depicted in Figure 1, partial Lewis acidic site originated from SO_4^{2-}/M_xO_y can be automatically transformed into Brønsted acidic site by absorbing H_2O. Depending on the synthetic procedures of solid acids SO_4^{2-}/M_xO_y reported by authors [37,38], we selected $SO_4^{2-}/\gamma\text{-}Al_2O_3$, SO_4^{2-}/TiO_2, and SO_4^{2-}/ZnO as acidic catalysts to investigate a model three-component Mannich reaction of among aniline, bezenyldehyde, and dimethyl malonate, as well as evaluate their catalytic activities, which were depicted in Table 1. It was found that under the same conditions, the effect of SO_4^{2-}/TiO_2 (prepared at 200°C, 300°C, and 400°C, respectively) utilized in the model three-component Mannich reaction, performing the better result of dimethyl 2-(phenyl(phenylamino)methyl)malonate **4**, with 45%–65% in yields (entries 4–9, in Table 1), was more than that of SO_4^{2-}/ZnO and $SO_4^{2-}/\gamma\text{-}Al_2O_3$, with 34% and 26% in yields (entries 2 and 3, in Table 1). In addition, we have known that SO_4^{2-}/TiO_2 prepared at different calcination temperatures are able to perform varied intensity of Lewis and Brønsted acidities. SO_4^{2-}/TiO_2 as solid acidic catalyst prepared at 200°C, 300°C, and 400°C, respectively, was studied on the above model three-component Mannich reaction to evaluate their catalytic activities. The results demonstrated that the

Table 1

The three-component Mannich reaction promoted by solid acids SO_4^{2-}/TiO_2.



1 2 3 4

Entry	Cat/mol%	Solvent	Temp./°C	Time/h	Yield/%[d]
1	—	DCM	rt	24	trace
2	SO_4^{2-}/ZnO[a]/10 mol%	DCM	rt	24	34
3	$SO_4^{2-}/\gamma\text{-}Al_2O_3$[a]/10 mol%	DCM	rt	24	26
4	SO_4^{2-}/TiO_2[a]/10 mol%	DCM	rt	24	45
5	SO_4^{2-}/TiO_2[b]/10 mol%	DCM	rt	24	55
6	SO_4^{2-}/TiO_2[c]/10 mol%	DCM	rt	24	61
7	SO_4^{2-}/TiO_2[c]/10 mol%	toluene	rt	24	64
8	SO_4^{2-}/TiO_2[c]/10 mol%	EtOH	rt	24	60
9	SO_4^{2-}/TiO_2[c]/20 mol%	toluene	rt	24	65
10	SO_4^{2-}/TiO_2[a]/10 mol%	xylene	rt	24	21[e]

[a]Prepared at 400°C.
[b]Prepared at 300°C.
[c]Prepared at 200°C.
[d]Isolated yield after chromatographic purification.
[e]SO_4^{2-}/TiO_2 refluxed for 6 h in xylene to be cool down to room temperature, with equipment of dean stark.

effect of calcination temperature of 200°C performs better than that of 300°C and 400°C in catalytic activity of SO_4^{2-}/TiO_2 under the same conditions. The resulting amino esters **4** exhibited dramatic distinctions in yields, with the yields of 61%, 55%, and 45%, respectively (entries 4–6, in Table 1). While practically no product formation was observed in the absence of any catalyst (entry 1, in Table 1). To optimize reaction conditions for performing better catalytic activity of SO_4^{2-}/TiO_2, we further studied this model reaction using solid acidic catalyst SO_4^{2-}/TiO_2 (prepared at 200°C) under different conditions. We discovered that toluene offered better yield (entry 7, in Table 1), as compared to other solvents such as EtOH or dichloromethane. Additionally, by increasing amount of solid acidic catalyst SO_4^{2-}/TiO_2 (prepared at 200°C) from 10 mol% to 20 mol% (entry 9, in Table 1), it did not enhance the yield significantly at the ambient temperature. What is more, we selected solid acidic catalyst SO_4^{2-}/TiO_2 (prepared at 400°C) to be refluxed for 6 h in solvent of xylene, with equipment of dean stark, that was aimed to evaporate water away from the SO_4^{2-}/TiO_2. In other words, it enabled to keep SO_4^{2-}/TiO_2 solid acid's Lewis acid sites, without Brønsted acid sites. It is obvious that the yield of product **4** decreased dramatically (entry 10, in Table 1). All in all, those tests proved that the Brønsted acid site of SO_4^{2-}/TiO_2 is much more dominant than the Lewis aid site in the three-component Mannich reaction (entries 4–6, 10, in Table 1).

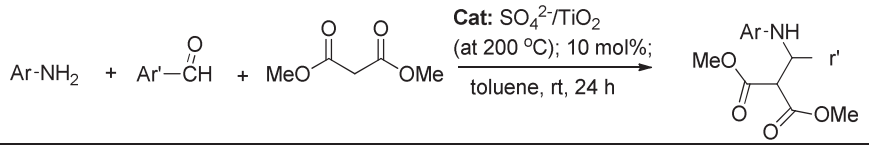
To further observe suitability of above mentioned solid acidic catalyst SO_4^{2-}/TiO_2, the next task was to evaluate the substrate scope, as shown as in Table 2. Utilization of SO_4^{2-}/TiO_2 (prepared at 200°C), performing excellent catalytic activity, to the three-component Mannich reaction, in order to investigate the scope of reaction with respect to aromatic primary amine and aldehyde, was done under the above optimum conditions. In view of the proposed ionization activation mode, primary amine was used as one of three components of Mannich reaction, which was regarded as a vital factor. Aromatic and heteroaromatic primary amines were possibly responsible for the effect of proposed ionization activation mode. When hetero aromatic primary amine bearing benzothiazol group was applied in the three-component Mannich reaction, it performed expectations to be less, with the range of 35%–49% in yields, as comparable to that of aromatic primary amine of aniline. To the best of our knowledge, heterocyclic ring primary amine could also offer additional proton acceptor, such as nitrogen, oxygen, and sulfur atom(s), which might disturb the effect of the ionization activation mode. To investigate the effect of aromatic aldehyde, the conjugated aromatic aldehyde reacted with mono-or non-substituted benzothiazol primary amine and dimethyl malonate to obtain resulting amino esters **12**, **13**, with 49% and 48% in yields was slightly different from non-conjugated aromatic aldehyde in yield, such as non- or mono-substituted benzaldehyde, 2-furfuraldehyde, and 2-formylthiophene, under the same conditions, which was shown in entries 1–6 of Table 2. Benzothiazol primary amine was regarded as specific hetero aromatic amine, which was sensitive to strong Brønsted acid in the reacting system. So, the reaction involving benzothiazol primary amine was not to be proceeded well by applying SO_4^{2-}/TiO_2 (prepared at 200°C), which had been in agreement with experiments. Therefore, various benzothiazol β-amino esters were afforded with not good conversion. Simultaneously, through refluxing for some hours in xylene, solid acid SO_4^{2-}/TiO_2 (prepared at 400°C) was able to exclude its Brønsted acid sites. It was proved that the solid acid SO_4^{2-}/TiO_2 (prepared at 400°C) excluded Brønsted acidic sites disable to promote the three-components Mannich reaction to carry on.

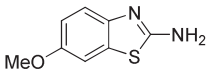
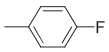
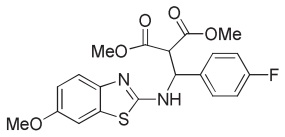
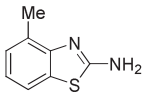
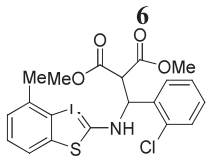
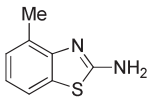
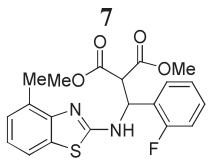
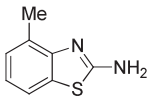
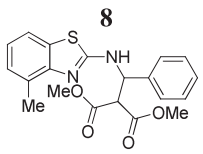
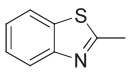
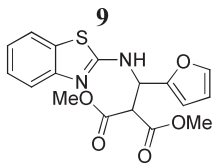
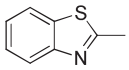
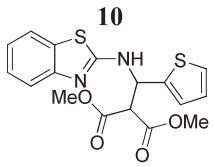
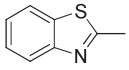
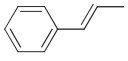
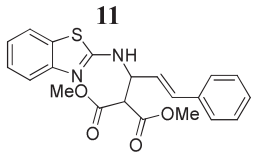
In repetition of solid acid SO_4^{2-}/TiO_2 (prepared at 200°C), the solid acid SO_4^{2-}/TiO_2 was filtrated out from the reaction system, and then promoted at calcination temperature of 200°C for 5 h. The renewed solid acid SO_4^{2-}/TiO_2 was reused in the same Mannich reaction of among aniline, bezenyldehyde, and dimethyl malonate under the conditions (entry 7, in Table 1) to evaluate its catalytic activity. The results showed that catalytic activity of renewed SO_4^{2-}/TiO_2 is still kept well, with 62% in yield of product **4**.

In order to account for ionization activation mode of the three-component Mannich reaction in the presence of solid acid SO_4^{2-}/TiO_2, we divided the three-component Mannich reaction into two steps: one is the condensation of aromatic primary amine with aromatic aldehyde to form intermediate of iminiums; the other is nucleophilic addition of dialkyl malonate to the former intermediate to afford β-amino esters product. Setting up a model condensation of aniline with benzyldehyde to obtain the intermediate of iminium N-benzylideneaniline **5** with using solid acidic catalyst SO_4^{2-}/TiO_2 (prepared at 200°C, 300°C, and 400°C, respectively) was made to evaluate their catalytic activities at room temperature, with stirring for 24 h in solvent of toluene, which was shown as in Table 3. The intermediate of N-benzylideneaniline **5** was afforded in yields of 63%, 61%, and 59%, respectively, which was purified by means of recrystallization with EtOH. It was indicated that in this model condensation, SO_4^{2-}/TiO_2 (prepared at 200°C), performing 6.964 (Brønsted acidity) and 1.568 (Lewis acidity) identified by area value of character peaks *in situ* FTIR pyridine adsorption spectrum, is not obvious difference from others prepared at 300°C (6.206 and 1.087 in Brønsted and Lewis acidities) and 400°C (4.990 and 0.870 in Brønsted and Lewis acidities) in catalytic activity [31]. Unfortunately, when Ar was benzothiazol

Table 2

The three-component Mannich reaction induced by solid acid SO_4^{2-}/TiO_2 (prepared at 200°C).

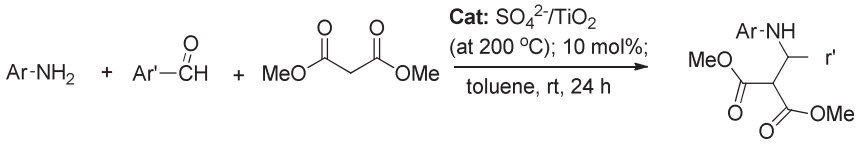


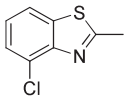
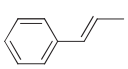
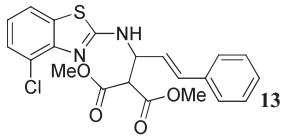
Entry	Ar	Ar′	Product	Yield/%[a]
1				37[b]
2			**6** 	35[b]
3			**7** 	39[b]
4			**8** 	37[b]
5			**9** 	35[b]
6			**10** 	38[b]
7			**11** 	49[b]
			12	

(*Continued*)

Table 2

(*Continued*)



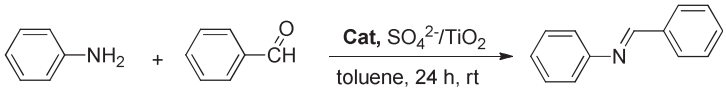
Entry	Ar	Ar′	Product	Yield/%[a]
8			 **13**	48[b]

13

[a]Isolated yield after chromatographic purification.
[b]Newly SO_4^{2-}/TiO_2 prepared at 200°C.

Table 3

The model condensation of aniline with benzyldehyde by applying SO_4^{2-}/TiO_2.



1 **2** **5**

Entry	**Cat**/mol%	Calcination temp./C	Yield/%[a]
1	—	—	Trace
2	SO_4^{2-}/TiO_2/10 mol%	200	63
3	SO_4^{2-}/TiO_2/10 mol%	300	61
4	SO_4^{2-}/TiO_2/10 mol%	400	59

[a]Isolated yield after chromatographic purification.

group, a series of benzothiazol imines derived from reaction of benzothiazol amines with non-conjugated or conjugated aromatic aldehydes in the presence of SO_4^{2-}/TiO_2 (prepared at 200°C, 300°C, and 400°C, respectively) at room temperature, eventually stirring for 48 h, was not detected by TLC. This evidence indicated that the plausible track of benzothiazol β-amino esters' condensation does not possibly follow product of dimethyl 2-(phenyl(phenylamino)methyl)malonate **4**.

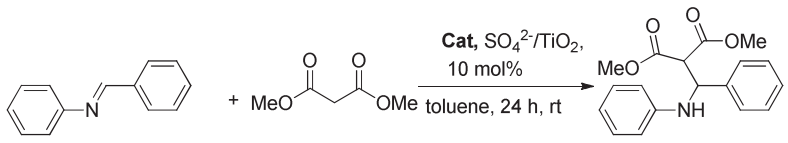
To the best of our knowledge, the condensation of aniline with benzyldehyde is actually nucleophilic addition–elimination. Conventionally, nucleophilic addition needs increased effective collisions between nucleophile and electrophile by heating up to reflux for several hours to form the intermediate of corresponding amino methanol, for example, phenyl(phenylamino) methanol. And then, the elimination of corresponding amino methanol is made to form carbon–nitrogen double bond (C═N) by taking off a H_2O in acidic environment, because of its hydroxyl group protonated to be good leaving group. Because of SO_4^{2-}/TiO_2 solid acid performing powerful Brønsted and Lewis acidities, benzyldehyde as electrophile was protonated to be activated in the reaction system. The activation energy of condensation of benzyldehyde with aniline was permitted to be lowered. Therefore, the above condensation was put into effect at room temperature.

What is more, in the step of formation of β-amino esters, the nucleophilic addition of dimethyl malonate to N-benzylideneaniline **5** to form product **4** was done in the presence of SO_4^{2-}/TiO_2 (prepared at 200°C, 300°C, and 400°C, respectively), the results were almost agreeable to corresponding data from entries 4–7, in Table 1, as shown as in Table 4.

In view of Figures 2 and 3, it was proposed that the two plausible mechanisms of Mannich transformation by acid or base were discussed. In acidic catalysis, SO_4^{2-}/TiO_2 offering strong Brønsted acidity can protonate the nitrogen atom of iminiums to be activated; subsequently, the active iminiums are attacked by less amount of enol of dimethyl malonate to complete Mannich transformation. Simultaneously, in base catalysis, wake

Table 4

The two-component Mannich reaction induced by applying SO_4^{2-}/TiO_2.



5 3 4

Entry	**Cat**/mol%	Calcination temp./°C	Yield/%[a]
1	—	—	Trace
2	SO_4^{2-}/TiO_2/10 mol%	200	66
3	SO_4^{2-}/TiO_2/10 mol%	300	61
4	SO_4^{2-}/TiO_2/10 mol%	400	58
5	NEt_3/10 mol%	—	15

[a]Isolated yield after chromatographic purification.

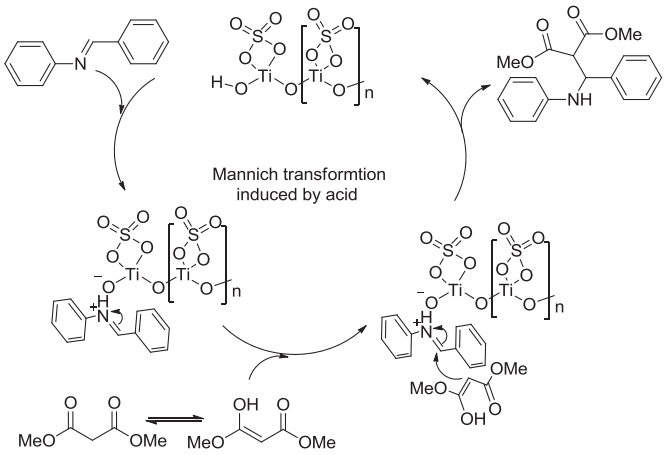


Figure 2. Proposed plausible mechanism of Mannich transformation induced by acid.

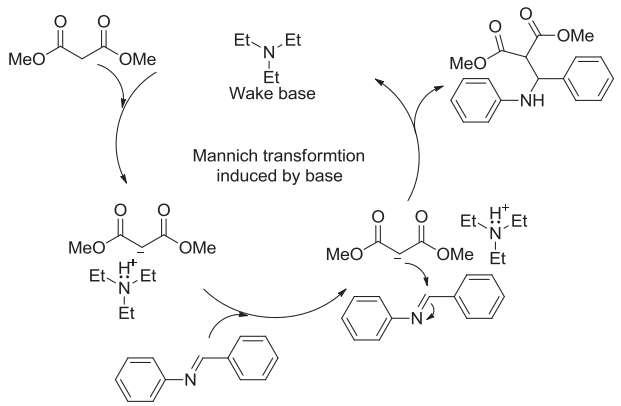


Figure 3. Proposed plausible mechanism of Mannich transformation induced by base.

base such as triethyl amine bearing a pair of lonely electrons can capture active proton originated from α-carbon of dimethyl malonate to be strong nucleophile, and then to attack un-activated iminiums to obtain *β*-amino esters. Comparing the two activation modes, the yield in acidic catalysis is more than that in basic catalysis under the same conditions. By which it indicates that active energy of the whole reaction in acid catalysis should be lower than that in base catalysis, which is depicted in **Table** 4.

CONCLUSIONS

The three-component Mannich reaction of among dimethyl malonate, aromatic primary amine, and aldehyde in the presence of solid acidic catalyst SO_4^{2-}/M_xO_y, especially for SO_4^{2-}/TiO_2 (prepared at 200°C, 300°C, and 400°C, respectively) was allowed to be continue at ambient temperature. Simultaneously, experimental data have proved the Brønsted acidity of SO_4^{2-}/TiO_2 to be dominant in the three-component Mannich reaction. Relying on this point, it successfully

proved that the effect of SO_4^{2-}/TiO_2 (prepared at 200°C) is much more than that of SO_4^{2-}/TiO_2 (prepared at 300°C and 400°C, respectively). In observing the mechanism of Mannich transformation induced by solid acid catalyst, we divided the three-component Mannich reaction into two steps: one is condensation of aromatic primary amine with aromatic aldehyde to form the intermediate of iminiums; the other is nucleophilic addition of dimethyl malonate to prepared iminiums to afford product. Taking the three-component Mannich reaction among aniline, bezenyldehyde, and dimethyl malonate for example, both of above two steps did work in the presence of SO_4^{2-}/TiO_2 as solid acidic catalyst, with moderate yields. Therefore, it was proposed that the plausible mechanism of the three-component Mannich reaction possibly undergoes formation of the intermediate of iminiums, subsequently, to be activated by protonation in the presence of SO_4^{2-}/TiO_2, as compared to the activation mode of base catalysis.

EXPERIMENTAL

General experimental procedure for the three-components Mannich reaction. Aromatic aldehyde (20 mmol) and solid acid SO_4^{2-}/TiO_2 loading 10 mol% (2 mmol, 0.3524 g) in dry toluene (5 mL) were added and stirred for 5 min at room temperature under argon atmosphere. And then, primary amine (16 mmol) and dimethyl malonate **3** (22 mmol) were added in turn, and the progress of the reaction was monitored by conducting thin layer chromatography on silica gel. After 24 h, the reaction was ended. The solid acid SO_4^{2-}/TiO_2 was filtered out from the reaction system. The organic phase was dried with anhydrous $MgSO_4$. After separation out of solid, the dry organic phase was evaporated away. The residue was submitted to column chromatography on silica gel (petroleum ether / EtOAc = from 10/1 to 5/1) to afford final product.

General experimental procedure for the two-component Mannich reaction.

The first step: aromatic aldehyde (20 mmol) and solid acid SO_4^{2-}/TiO_2 loading 10 mol% (2 mmol, 0.3524 g) in dry toluene (5 mL) were added and stirred for 5 min at room temperature under argon atmosphere. And then, primary amine (16 mmol) was added, and the progress of the reaction was monitored by conducting thin layer chromatography on silica gel. After 24 h, the reaction was ended. The solid acid SO_4^{2-}/TiO_2 was filtered out from the reaction system. The organic phase was dried with anhydrous $MgSO_4$. After separation out of solid, the dry organic phase was evaporated away. The residue was submitted to column chromatography on silica gel (petroleum ether / EtOAc =10/1) to afford intermediate of imines.

The second step: a mixture of imines (20 mmol) and solid acid SO_4^{2-}/TiO_2 loading 10 mol% (2 mmol, 0.3524 g) in dry toluene (5 mL) was stirred for 5 min at room temperature under argon atmosphere. And then, dimethyl malonate 3 (22 mmol) was added dropwise, and the progress of the reaction was monitored by conducting thin layer chromatography on silica gel. After 24 h, the reaction was ended. The solid acid SO_4^{2-}/TiO_2 was filtered out from the reaction system. The organic phase was dried with anhydrous $MgSO_4$. After separation out of solid, the dry organic phase was evaporated away. The residue was submitted to column chromatography on silica gel (petroleum ether / EtOAc = from 10/1 to 5/1) to afford final product.

Dimethyl 2-(phenyl(phenylamino)methyl)malonate (5). As a white solid; yield: 64%; M.p. 98–100°C. ^{1}H–NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 8.04 (d, *J* = 10, 1H), 7.79 (d, *J* = 10 Hz, 1H), 7.53–7.48 (m, 4H), 7.34–7.26 (m, 3H), 7.23 (d, *J* = 5 Hz, 1H), 7.18 (t, *J* = 10 Hz, 1H), 6.41–6.39 (d, *J* = 10 Hz, 1H), 5.53–5.49 (t, *J* = 20 Hz, 1H), 4.97–4.91 (dd, *J* = 20 Hz, 1H), 4.17–3.98(m, 4H), 1.30 (t, *J* = 5 Hz, 3H), 1.15 (t, *J* = 5 Hz, 3H); ^{13}C–NMR (125 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 141.3(d), 135.6, 134.3, 128.7, 127.7(d), 126.3, 125.9, 125.2, 123.9, 120.1, 118.6, 63.5(d), 56.9, 55.7; *Anal*. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.43; H, 5.85; N, 5.14.

Dimethyl-2-((6-methoxybenzo[d]thiazol-2-ylamino)(4-fluorophenyl)methyl)malonate (6). As a colorless oil; yield: 12%; ^{1}H–NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 7.43–7.36 (m, 3H), 7.07 (d, *J* = 2.9 Hz, 1H), 7.00 (t, *J* = 8.6 Hz, 2H), 6.89–6.84 (m, 2H), 5.68–5.63 (m, 1H), 3.98 (d, *J* = 5.2 Hz, 1H), 3.78 (m, 3H), 3.71 (s, 3H), 3.65 (s, 3H); ^{13}C–NMR (125 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 168.5, 167.3, 164.3, 163.4, 161.6, 155.7, 146.3, 134.6, 131.9, 128.6, 128.3, 120.0, 116.1, 115.5, 113.8, 105.4, 56.9, 55.9, 53.2, 52.9; ^{19}F–NMR (470 MHz, $CDCl_3$): δ (ppm) −113.9. *Anal*. Calcd for $C_{20}H_{19}FN_2SO_5$: C, 57.41; H, 4.58; N, 6.69. Found: C, 57.43; H, 4.75; N, 6.74.

Dimethyl 2-((4-methylbenzo[d]thiazol-2-ylamino)(2-chlorophenyl) methyl)malonate (7). As a colorless oil; yield:23%; ^{1}H–NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 7.49–7.41 (m, 1H), 7.40–7.33 (m, 2H), 7.27–7.21 (m, 3H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.4 H z, 1H), 5.92 (q, *J* = 4.6 Hz, 1H), 4.19 (d, *J* = 4.6 Hz, 1H), 3.76 (m, 3H), 3.67 (s, 3H), 2.52 (s, 3H); ^{13}C–NMR (125 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 168.5, 167.4, 165.3, 151.2, 129.9, 129.7, 128.5, 127.1, 126.8, 121.9, 118.5, 55.9, 54.2, 52.9, 18.6. *Anal.* Calcd for $C_{20}H_{19}ClN_2SO_4$: C, 57.34; H, 4.57; N, 6.69. Found: C, 57.21; H, 4.94; N, 6.70.

Dimethyl-2-((4-methylbenzo[d]thiazol-2-ylamino)(2-fluorophenyl)methyl)malonate (8). As a colorless oil, yield: 25%; ^{1}H–NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 7.46 (t, *J* = 7.4 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.23–7.31 (m, 1H), 7.05 (q, *J* = 7.4 Hz, 3H), 6.99 (t, *J* = 8.0 Hz, 1H),

6.84 (d, J = 9.2 Hz, 1H), 5.81–5.88 (m, 1H), 4.14 (d, J = 5.7 Hz, 1H), 3.69 (s, 3H), 3.70 (m, 3H), 2.54 (s, 3H); ^{13}C–NMR (125 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 168.3, 167.3, 165.2, 161.7, 159.8, 151.4, 128.7, 126.8, 124.5, 122.0, 118.4, 115.9, 115.4, 53.6, 53.2, 18.4; ^{19}F–NMR (470 MHz, $CDCl_3$): δ (ppm) −117.7. *Anal*. Calcd for $C_{20}H_{19}FN_2SO_4$: C, 59.69; H, 4.76; N, 6.96. Found: C, 59.27; H, 4.51; N, 6.79.

Dimethyl 2-((4-methylbenzo[d]thiazol-2-ylamino)(phenyl)methyl) malonate (9). As a colorless oil, yield: 37%, ^{1}H–NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 7.41–7.37 (m, 3H), 7.33 (t, J = 7.7 Hz, 2H), 7.27 (t, J = 6.3 Hz, 1H), 7.07 (d, J = 6.9 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 6.87 (br, 1H), 5.64–5.63 (m, 1H), 4.04–4.03 (m, 1H), 3.68 (s, 6H), 2.52 (s, 3H); ^{13}C–NMR (125 MHz, $CDCl_3$, 25°C, TMS): δ (ppm) 168.3, 167.3, 165.4, 151.2, 138.6, 129.2, 128.9, 128.2, 126.7, 126.6, 121.7, 118.3, 58.4, 57.0, 53.2, 52.9, 18.4; *Anal*. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found: C, 62.43; H, 5.27; N, 7.40.

Dimethyl 2-((benzo[d]thiazol-2-ylamino)(furan-2-yl)methyl) malonate (10). As a white solid; yield: 35%; M.p. 102–103°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.55–7.58(t, 2H), 7.29–7.34(m, 2H), 7.08–7.11(t, 1H), 6.61(s, 1H), 6.29–6.32(dd, 2H), 5.87(d, J = 4.6 Hz, 1H), 4.18(d, J = 4.6 Hz, 1H), 3.75(s, 3H), 3.71(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.42, 167.12, 165.92, 152.17, 151.33, 142.53, 130.95, 126.00, 122.15, 120.91, 119.59, 110.71, 107.72, 54.09, 53.22, 52.99, 52.46. *Anal*. Calcd for $C_{17}H_{15}N_2O_5S$: C, 56.82; H, 4.21; N, 7.80; Found: C, 56.57; H, 4.14; N, 7.68.

Dimethyl 2-((benzo[d]thiazol-2-ylamino)(thiophen-2-yl)methyl) malonate (11). As a white solid; yield: 33%; M.p. 105–107°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):7.54–7.57(t, 2H), 7.25–7.30(m, 1H), 7.20(d, J = 5.2 Hz, 1H), 7.07–7.10(t, 1H), 7.04(d, J = 3.4 Hz, 1H), 6.92–6.93(t, 1H), 6.88(s, 1H), 6.04(s, 1H), 4.13(d, J = 4.6 Hz, 1H), 3.71(s, 3H), 3.74(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):168.48, 167.02, 165.83, 152.13, 142.37, 130.96, 127.13, 126.00, 125.37, 122.13, 120.93, 119.58, 56.78, 54.25, 53.27, 53.06. *Anal*. Calcd for $C_{17}H_{15}N_2O_4S_2$: C, 54.38; H, 4.03; N, 7.46; Found: C, 54.23; H, 4.05; N, 7.41.

Dimethyl-2-(1-(benzo[d]thiazol-2-ylamino)-3-phenylallyl) malonate (12). As a colorless oil; yield: 39%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.55–7.58(t, 2H), 7.22–7.36(m, 6H), 7.07–7.11(t, 1H), 6.71(d, J = 16 Hz, 1H), 6.27–6.31(dd, 1H), 5.28(s, 1H), 4.09–4.14(q, 1H), 3.96(d, J = 4.6 Hz, 1H), 3.78(s, 3H), 3.72(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.41, 167.58, 166.04, 135.96, 133.22, 130.46, 128.67, 128.25, 126.81, 126.04, 125.33, 122.06, 120.92, 119.36, 56.53, 55.40, 53.13, 52.97; *Anal*. Calcd for $C_{21}H_{19}N_2O_4S$: C, 63.78; H, 4.84; N, 7.08; Found: C, 63.36; H, 5.26; N, 7.11.

Dimethyl 2-(1-((4-chlorobenzo[d]thiazol-2-yl)amino)-3-phenylallyl) malonate (13). As a colorless oil; yield: 38%; ^{1}H NMR (500 MHz $CDCl_3$) δ (ppm): 7.22–7.53(m, 9H), 6.70(d, J = 16 Hz, 1H), 6.25–6.31(dd, 1H), 5.26–5.29(m, 1H), 3.94 (d, J = 4.6 Hz, 1H), 3.78(s, 3H), 3.72(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.42, 167.51, 166.10, 150.89, 135.88, 133.35, 132.00, 128.69, 128.31, 127.15, 126.81, 126.46, 125.15, 120.55, 120.02, 56.49, 55.32, 53.15, 52.99; *Anal*. Calcd for $C_{21}H_{18}N_2O_4ClS$: C, 58.67; H, 4.22; N, 6.52; Found: C, 58.16; H, 3.98; N, 6.21.

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