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PII: S0040-4020(18)31229-8

DOI: 10.1016/j.tet.2018.10.023

Reference: TET 29856

To appear in: *Tetrahedron*

Received Date: 17 September 2018

Revised Date: 11 October 2018

Accepted Date: 12 October 2018

Please cite this article as: Kitanosono T, Cho SM, Kobayashi Shū, A convenient and mild cyclocondensation using water-soluble aldehydes in water, *Tetrahedron* (2018), doi: https://doi.org/10.1016/j.tet.2018.10.023.

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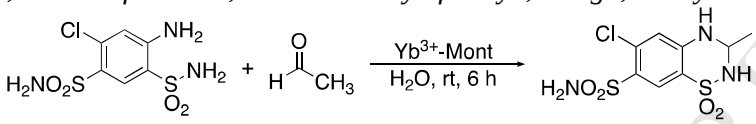

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A convenient and mild cyclocondensation using water-soluble aldehydes in water

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Reaction in water
Montmorillonite
Cyclocondensation
Thiazide
Ytterbium

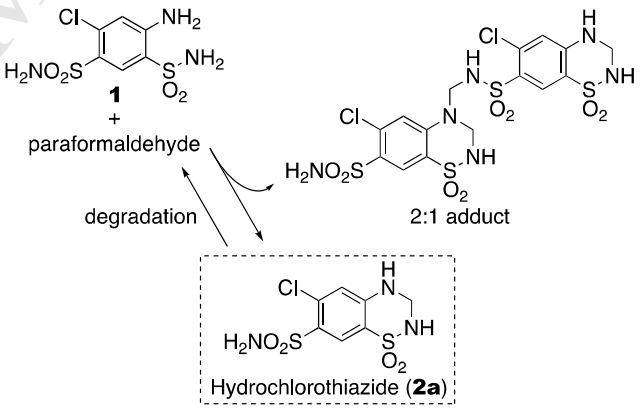
ABSTRACT

The use of negatively charged aluminosilicate layers and Lewis acidic cations embedded therein allowed efficient cyclocondensation of bisamines with water-soluble aldehydes to be achieved in water. The protocol does not involve acidic or reflux conditions, thereby avoiding undesired byproduct formation. The use of water as a reaction medium is indispensable to ensure high reaction yields.

1. Introduction

Heterocyclic compounds have been recognized as a vital class of organic compounds for the biological processes of living organisms. Among these compounds, quinazolinones, quinolinones, and thiazides, which can be formally derived from a Schiff base (generated from aldehydes) and subsequent cyclization, have attracted considerable attention because they provide a cornucopia of drug candidates due to their broad and efficient bioactivities including carcinostatic, anti-inflammatory, antimicrobial, antiviral, anti-cytotoxin, antiepileptic, antipsychotic, and antihypertensive actions.[1-5] In spite of the simplicity of their synthesis, an efficient catalytic process that allows rapid access to their derivatives under mild conditions remains highly desirable for medicinal chemistry and organic synthesis.

Although hydrochlorothiazide (HCTZ; **2a**) has been used as a diuretic drug for more than half a century, it can contain impurities formed during its production or its degradation. The European Pharmacopoeia recommends that total impurity should not be more than 1%.[6] Although elevated temperature and acid catalysts have often been used for its production,[7-9] the thiazide skeletons are known to undergo degradation at high temperature.[10-12] One of the impurities generated during the synthesis is the 2:1 HCTZ-formaldehyde adduct.[13]



Scheme 1. Hydrochlorothiazide degradation and byproduct formation during its synthesis.

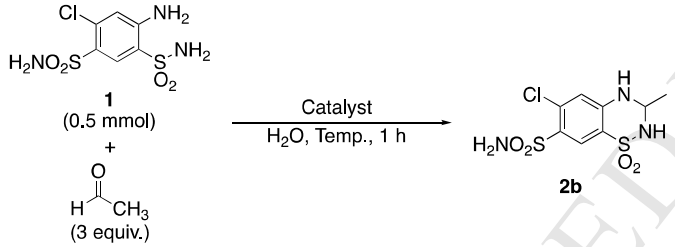
We therefore wanted to develop a highly active catalyst that would allow the reactions to be performed under mild conditions, and that would suppress undesired degradation and byproduct formation. Our envisioned design relies on the anionic stabilization of cationic iminium intermediates coupled with Lewis acidic activation of aldehyde molecules. The use of water as a reaction medium is another tactic to facilitate the Schiff base formation.[14] Ion-exchanged montmorillonites embody an exquisite balance of intrinsically anionic scaffold whose negative charge is delocalized along the aluminosilicate unit layers with Lewis acidic nature to avoid their incompatibility.

2. Results and discussion

We commenced our investigation with the use of ion-exchanged montmorillonites in water for the reaction of

chloraminophenamide **1** with acetaldehyde (Table 1). With **1** being very slightly soluble in water, the reaction proceeded sluggishly with H^+-exchanged montmorillonite (entry 1). On the other hand, aqueous hydrochloric acid provided methiazide **2b** in almost the same yield (entry 2), suggesting little involvement of the Brønsted acidity of the montmorillonite in the reaction. In contrast, sodium montmorillonite (Na^+-Mont), a naturally occurring clay, afforded **2b** in much higher yield (entry 3). Significantly decreased catalytic activity of mesoporous sodium *beta*-zeolite, sodium dodecylsulfate as a surfactant, and sodium trifluoromethanesulfonate (entries 4, 6) implied the important role of the negatively charged aluminosilicate layer to facilitate the reaction. Among the first-row transition-metal cation-exchanged montmorillonites, Zn^{2+}-Mont showed the same activity as Na^+-Mont (entries 7–9). Given that increased loading of Zn^{2+} resulted in a significant decrease in the reaction yield of **2b**, we conclude that Zn^{2+}-Mont is not a suitable catalyst (entry 10). Similarly, Yb^{3+}-Mont exhibited a catalytic performance as good as that of Na^+-Mont (entry 11). Unlike Zn^{2+}-Mont, Yb^{3+}-Mont exhibited constant catalytic performance (entry 12). Furthermore, it was found that the reaction catalyzed by Yb^{3+}-Mont resulted in almost equal conversion even at room temperature within 6 h (entry 13), whereas the reaction furnished only 10% yield of **2b** without any catalyst. When ytterbium triflate was used instead of Yb^{3+}-Mont, the reaction suffered from low yield because there was no anionic scaffold to facilitate the reaction (entry 14). Finally, longer reaction time led to the quantitative formation of **2b** (entry 15).

Table 1
Ion-exchanged montmorillonite-catalyzed formation of **2b** in water.

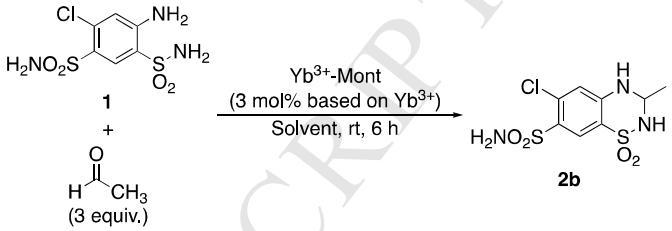


Entry	Catalyst	Temp. (°C)	Yield (%)[a]
1	H^+-Mont	40	12
2	HCl (5 mol%)	40	15
3	Na^+-Mont (Na: 1.19 mmol/g)[b]	40	65
4	Na^+-*beta*-Zeolite (JRC 150)[b]	40	24
5	$NaOSO_3C_{12}H_{25}$ (12 mol%)	40	12
6	NaOTf (12 mol%)	40	8
7	Sc^{3+}-Mont (Sc: 0.31 mmol/g)[b]	40	32
8	Cu^{2+}-Mont (Cu: 0.30 mmol/g)[b]	40	48
9	Zn^{2+}-Mont (Zn: 0.30 mmol/g)[b]	40	66
10	Zn^{2+}-Mont (Zn: 0.45 mmol/g)[b]	40	54
11	Yb^{3+}-Mont (Yb: 0.29 mmol/g)[b]	40	64
12	Yb^{3+}-Mont (Yb: 0.34 mmol/g)[b]	40	61
13[c]	Yb^{3+}-Mont (Yb: 0.34 mmol/g)[b]	rt	57
14[c]	$Yb(OTf)_3$ (3 mol%)	rt	9
15[d]	Yb^{3+}-Mont (Yb: 0.34 mmol/g)[b]	rt	>99

[a] Based on NMR spectroscopic analysis. [b] 50 mg of catalyst was used. [c] For 6 h. [d] For 12 h.

A range of solvents were evaluated in the reaction catalyzed by Yb^{3+}-Mont at ambient temperature to verify the superiority of water as a reaction medium (Table 2). Only when ethanol, acetonitrile, or ethyl acetate was used did sulfonamide **1** clearly dissolve together with acetaldehyde. However, almost no product was formed in ethanol, presumably because of the higher stability of the acetal form (entry 1). The catalyst showed relatively high activity in acetonitrile and ethyl acetate, which facilitated the release of the product from the catalyst (entries 2 and 3). Both reactions were nevertheless found to reach a plateau phase before even one-half of the reactant was consumed. Other solvents in which **1** was immiscible resulted in sluggish reactions, except water (entries 5–8). When water was used, the reaction was faster than that in either acetonitrile or ethyl acetate and reached 100% completion (entry 4). No formation of byproducts derived from **1** or aldol condensation of acetaldehyde was observed under any of the conditions used.

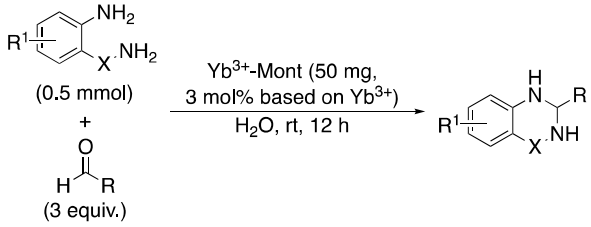
Table 2
Effect of solvents.

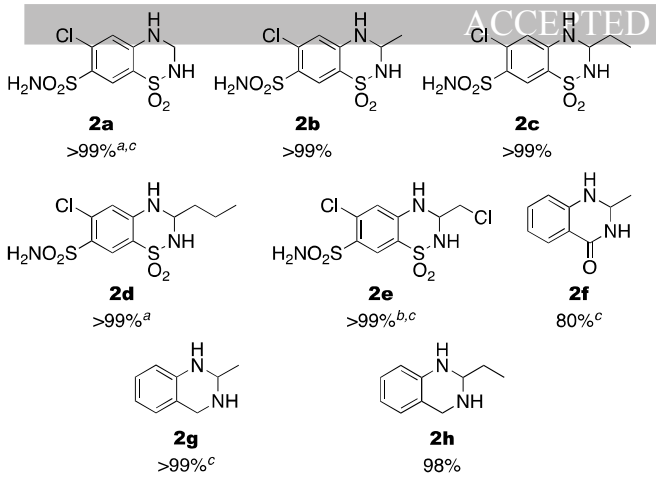


Entry	Solvent	Yield (%)[a]
1	ethanol	trace
2	acetonitrile	34 (39)[b]
3	ethyl acetate	48 (45)[b]
4	water	57 (>99)[b]
5	hexane	trace
6	chloroform	trace
7	dichloromethane	10
8	diethyl ether	trace

[a] Based on NMR spectroscopic analysis. [b] For 12 h.

With optimized conditions in hand, the scope of the reaction with respect to substrates was investigated (Scheme 2). The catalyst was suitable for the quantitative synthesis of HCTZ **2a**, ethiazide **2c**, and prothiazide **2d**. The reaction proceeded quantitatively with chloroacetaldehyde to provide **2e**. As represented by trichloromethiazide, chlorine-substitution is found in some pharmaceuticals, and the monochloromethyl analogue exhibited slightly higher activity.[15] 2-Aminobenzylamide and 2-aminobenzylamine reacted with water-soluble aldehydes in high yields (**2f–h**).



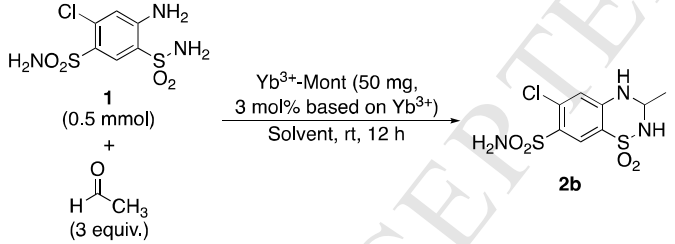


[a] Performed at 60 °C for 1 h. [b] Performed at 60 °C for 6 h. [c] With 6 equivalents of aldehyde.

Scheme 2. Scope of substrates.

The Yb^{3+}-Mont was found to be amenable to easy catalyst recovery and reuse (Table 3), although Na^{+}-Mont is known to form an aqueous emulsion with certain amounts of water.[16] When Yb^{3+}-Mont was recovered by simple filtration after the first run, the catalyst could be recovered completely with almost no Yb^{3+} leached out in the filtrate. After sufficient washing with water and ethyl acetate and subsequent drying *in vacuo*, the recovered catalyst was used in the second run. The recovered catalyst showed high reactivity, albeit with some weight loss during the workup procedure after the reaction. Given that the Yb^{3+} content of the filtrate was under the detection limit, the weight loss of the catalyst could result from handling issues. Meanwhile, 40% and >99% of catalyst were recovered after the first run in acetonitrile and ethyl acetate, respectively, albeit with much lower yield of **2b**.

Table 3
Recovery and reuse experiments.



Reaction cycle	Reaction medium	Yield (%)[a]	Yb^{3+} leaching (%)[b]	Catalyst recovery (%)[c]
1st	water	Quant	0.1	>99
2nd	water	97	UDL	88
1st	acetonitrile	39	–[d]	40
1st	ethyl acetate	45	–[d]	>99

[a] Based on NMR spectroscopic analysis. [b] Based on ICP analysis of the filtrate. [c] Calculated based on the weight of recovered catalyst. [d] Not measured.

Powder XRD analysis provided structural insights on Yb^{3+}-Mont (Figure 1). The interlayer spacing can be estimated by considering the sheet thickness of aluminosilicate (9.6 Å).[17-18] The *d* value calculated from the peak of Yb^{3+}-Mont corresponding to the (001) peak of the parent Na^{+}-Mont[16] increased by 0.2 Å (a and b). Given that all (*k l m*) peaks of the parent Na^{+}-Mont were still observed in Yb^{3+}-Mont, the aluminosilicate unit layers in Yb^{3+}-Mont retain multilayered regularity. When soaked with water, the interlayer space of Yb^{3+}-Mont expanded from 5.5 Å to 10.0 Å (c). Given that the space expansion on adsorbing water was also reported as a feature of Sc^{3+}-Mont and Cu^{2+}-Mont,[19,20] Yb^{3+}-Mont is expected to adopt a Yb^{3+} aqua complex enwrapped by aluminosilicate layers. Thermal treatment of Yb^{3+}-Mont after the reaction in water gave material with spectra that corresponded to the original state (d), consistent with a reversible hydration/dehydration process. The XRD pattern of water-adsorbed Yb^{3+}-Mont was retained even when filtration was carried out during the reaction (e). The interlayer spacing of 10.0 Å is sufficient for the reaction to take place.[21] The complex set of peaks is attributed to sulfonamide **1** and product **2b**.[22-23] The space expansion means that the reaction takes place in the interlayer space as expected to exploit both negatively charged aminosilicate layers and Lewis acidic site. In addition, it also means that the catalyst becomes relatively fragile, which is why centrifugation after the reaction resulted in loss of catalyst and significant Yb^{3+} leaching (ca. 20%) and quite poor reproducibility in the second run.

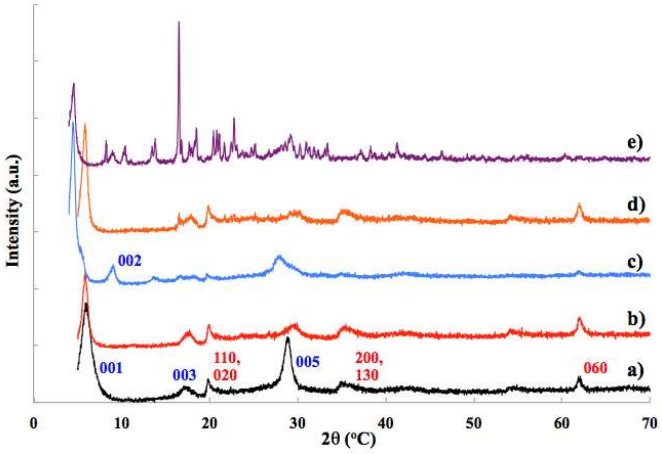


Figure 1. XRD patterns of the montmorillonites a) Na^{+}-Mont; b) Yb^{3+}-Mont; c) Yb^{3+}-Mont soaked with water; d) recovered Yb^{3+}-Mont after drying *in vacuo*; e) Yb^{3+}-Mont recovered by filtration during the reaction.

3. Conclusion

The Yb^{3+}-exchanged montmorillonite was found to be an efficient catalyst for cyclocondensation. The negatively charged aluminosilicate layers coupled with Lewis acidic nature contribute to facilitate the reaction, and the use of water as a reaction medium is highly beneficial. The catalytic system was applicable to the synthesis of diuretic drugs and derivatives, eschewing the use of a stoichiometric amount of acid and reflux conditions that have been used conventionally.

4. Experimental section

4.1. General information

Nuclear magnetic resonance (NMR) spectra were recorded with a JEOL ECA-500 spectrometer, operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C NMR in DMSO-d_6 unless otherwise noted. DMSO-d_6 served as the internal standard (δ = 2.50 ppm) for ^{1}H NMR and (δ = 39.1 ppm) for ^{13}C NMR. IR spectra were measured with a Shimadzu IRSpirit spectrometer. Melting points were determined with a Yazawa micro melting point BY-1 apparatus and are uncorrected. High-resolution mass spectra (HRMS) were recorded with a JEOL JMS-T100TD (ESI)

spectrometer. Column chromatography was carried out with Silica Gel 60 N (spherical, neutral) from Kanto Chemical Co., Inc. Deionized water from a Millipore Milli-Q machine (Gradient A 10) was used as solvent without further treatment. All organic solvents used were commercially available anhydrous solvents, which were distilled appropriately under an argon atmosphere or were stored over molecular sieves prior to use. All reagents used as substrates were either distilled or recrystallized before use. Centrifugation was performed with a Kokusan H-36 centrifuge at 3,500 rpm. X-ray diffraction was recorded with a Rigaku Miniflex 300/600 diffractometer machine with Cu Kα (λ =0.15406 nm) radiation at 40 kV and 40 mA. Na^+-Mont was purchased from Kunipia F, Kunimine Industry Co. Ltd. Ion-exchanged Zeolite was prepared from JRC H-*beta*-zeolite 150, (Si/Al = 150). 4-Amino-6-chloro-*m*-benzenedisulfonamide (**1**) was provided by Towa Pharmaceutical Co. Ltd. Ion-exchanged montmorillonites were prepared from 1.5 g of Na^+-Mont by stirring in 100 mL of aqueous $M(OTf)_3$ solution (5.0×10^{-3} M) at 50 °C for 24 h, and subsequent centrifugation at 3,500 rpm for 5 min, repeated washing with distilled water, and drying at 110 °C. Metal loading in Montmorillonite catalyst was determined by inductively coupled plasma (ICP) analysis with Shimadzu ICPS-7510 equipment, as follows. Catalyst (10-15 mg) was dissolved in 2–3 mL of hydrofluoric acid (**CAUTION**) at room temperature. When the catalyst was completely dissolved, the solution was diluted to 50 mL with pure water.

4.2. General procedure for cyclocondensation catalyzed by Yb^{3+}-Mont in water

Yb^{3+}-Mont was pretreated at 200 °C under vacuum for 2 h, immediately before the reaction. To pretreated Yb^{3+}-Mont (50 mg, 3 mol% based on Yb^{3+}) were added 4-amino-6-chloro-*m*-benzenedisulfonamide (**1**) (142.9 mg, 0.5 mmol), acetaldehyde (66.1 mg, 3.0 equiv.), and water (10 mL), and the mixture was stirred for 12 h at room temperature. The catalyst was separated by filtration and washed with ethyl acetate. Brine was added to the filtrate and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. During optimization of the reaction conditions, yields were determined based on the characteristic peak of the product using dibromomethane as an internal standard. Isolated yields are given unless otherwise noted.

*4.2.1. 6-Chloro-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide) (Hydrochlorothiazide, **2a**)[24]*

White solid; mp 273–276 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ = 4.75 (s, 2H), 7.00 (s, 1H), 7.53 (brs, 2H) 8.02-8.04 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 54.3, 117.0, 118.5, 125.5, 127.9, 134.3, 146.6.

*4.2.2. 6-Chloro-3-methyl-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide) (Methiazide, **2b**)[25]*

White solid; mp 258–261 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ = 1.45 (d, *J* = 6.2 Hz, 3H), 4.88-4.93 (m, 1H), 6.94 (s, 1H), 7.50 (s, 2H), 7.85 (d, *J* = 11.7 Hz, 1H), 7.98 (s, 1H), 8.01 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ = 19.7, 62.6, 116.9, 117.9, 125.5, 128.1, 134.4, 146.6; HRMS (ESI): *m*/*z* calcd. for $C_8H_{10}ClN_3O_4S_2$ $[M+H]^+$ 311.9880, found 311.9896.

*4.2.3. 6-Chloro-3-ethyl-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide) (Ethiazide, **2c**)[25]*

White solid; mp 269–270 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 0.99 (t, *J* = 7.4, 3H), 1.71-1.84 (m, 2H), 4.67 (s, 1H), 6.98 (s, 1H), 7.49 (s, 2H), 7.74 (brs, 1H). 7.91 (s, 1H), 7.97 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 9.1, 26.5, 67.2, 117.1, 118.2, 125.6, 128.1, 134.4, 146.6; HRMS (ESI): *m*/*z* calcd for $C_9H_{12}ClN_3O_4S_2$ $[M+H]^+$ 326.0036, found 326.0046.

*4.2.4. 6-Chloro-3-propyl-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide) (Prothiazide, **2d**)[25]*

White solid; mp 253–257 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 0.99-1.01 (m, 3H), 1.73-1.82 (m, 2H), 4.65-4.69 (m, 1H), 6.98 (s, 1H), 7.49 (s, 2H), 7.74 (d, *J* = 11.7, 2H). 7.91 (s, 1H), 7.97 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ = 9.1, 26.5, 67.2, 117.0, 118.2, 125.5, 128.1, 134.3, 146.6; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{14}ClN_3O_4S_2$ $[M+H]^+$ 340.0193, found 340.0174.

*4.2.5. 6-Chloro-3-(chloromethyl)-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide (**2e**)[26]*

White solid; mp 249–253 °C; IR (neat): ν = 736, 964, 1063, 1155, 1342, 1496, 1595, 3182, 3349, 3423 cm^{-1}; ^{1}H NMR (DMSO-d_6, 600 MHz): δ = 3.87 (d, *J* = 5.67 Hz, 2H), 4.99-5.04 (m, 1H), 7.06 (s, 1H), 7.54 (s, 2H), 7.99 (s, 1H), 8.10 (d, *J* = 11.3 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 43.7, 66.4, 117.3, 118.4, 125.2, 128.8, 134.6, 146.1; HRMS (ESI): *m*/*z* calcd for $C_8H_9Cl_2N_3O_4S_2$ $[M+H]^+$ 345.9490, found 345.9519.

*4.2.6. 2-Methyl-2,3-dihydroquinazolin-4(1H)-one (**2f**)[27]*

White solid; mp 137–141 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.40-1.43 (m, 3H), 4.29 (s, 1H), 4.97 (d, *J* = 4.0, 1H) 6.60 (d, *J* = 7.9, 1H), 6.78 (t, *J* = 7.4, 1H), 6.87 (s, 1H), 7.20-7.24 (m, 1H), 7.81 (d, *J* = 4.0, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.7, 61.6, 114.7, 115.9, 119.4, 128.5, 133.7, 147.6, 165.7.

*4.2.7. 2-Methyl-1,2,3,4-tetrahydroquinazoline (**2g**)[28]*

Yellow solid; mp 62–69 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ = 1.14-1.16 (m, 3H), 3.70 (d, *J* = 16.5 Hz, 1H), 3.86 (d, *J* = 16.5 Hz, 1H), 4.06 (q, *J* = 5.7 Hz, 1H), 5.69 (s, 1H), 6.41-6.48 (m, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ = 22.8, 45.8, 62.2, 113.8, 115.8, 120.5, 123.9, 126.5 144.7.

*4.2.8. 2-Ethyl-1,2,3,4-tetrahydroquinazoline (**2h**)[29]*

Yellow solid; mp 84–88 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.97 (t, *J* = 7.6 Hz, 3H), 1.53-1.57 (m, 2H), 3.88 (d, *J* = 16.5 Hz, 1H), 4.01 (t, *J* = 5.8 Hz, 1H), 4.06 (d, *J* = 16.5 Hz, 1H), 6.44 (d, *J* = 8.3 Hz, 1H), 6.60 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ = 9.2, 29.4, 46.5, 68.0, 114.9, 117.9, 121.5, 126.1, 127.1, 143.7.

4.3. General procedure for recovery and reuse experiments

After the first run, catalyst was filtered and washed with a small amount of distilled water. Half the amount of filtrate was taken out and, after sulfuric acid (1 mL) was added, the resulting solution was diluted in pure water (50 mL) and submitted to ICP analysis. The other half was used to determine the yield of the reaction. To this aqueous solution was added ethyl acetate (5–10 mL) and the mixture was stirred vigorously. The organic phase was extracted and this procedure was repeated until no substrate remained in the aqueous layer. The recovered catalyst was dried under vacuum for 6 h at room temperature, pretreated at 200 °C for 2 h and was reused for the next run.

Acknowledgments

This work was partially supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS), Global COE Program, The University of Tokyo, MEXT, Japan, and Japan Science Technology Agency (JST).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/xxxx.

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