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Montmorillonite K10: an effective catalyst for synthesis of 2-aminothiazoles

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Abstract An efficient one-pot synthesis of 2-aminothiazoles from methylcarbonyl and thiourea has been developed using montmorillonite-K10 as a catalyst at 80 °C in DMSO medium. A plausible mechanism is proposed in which α-iodomethyl-carbonyls are formed via methylcarbonyls as raw material using iodine as iodination reagent.

Keywords Montmorillonite-K10 · 2-Aminothiazole · Thiourea · Methylcarbonyls · Iodine

Introduction

Thiazole (or 1,3-thiazole) is one of the members of the azole families [1]. Thiazole and its derivatives are one of the main components in a variety of natural compounds [2]. Meanwhile, 2-aminothiazole derivatives as a subgroup of thiazole family are important because of their medical applications as anti-HIV, antidiabetic, antibacterial, antifungal, anti-oxidant, antitubercular, anti-inflammatory, anticancer, antihypertensive, and neuroprotective [3–8]. Also, there is an appropriate attention to this class of compounds in synthetic organic and medicinal chemistry. There are various ways to synthesize this category of compounds (Fig. 1) [9–18]. Each of the methods listed in Fig. 1 has positive and negative features; however, it seems that the use of methyl carbonyl and thiourea as precursors is the most convenient method.

In 2012, Wu and his colleagues proposed their method for the synthesis of 2-aminthiazole via a direct way using a CuO/I_2 system and acetophenone and thiourea as raw materials [19]. Although the scope of raw materials for aromatic

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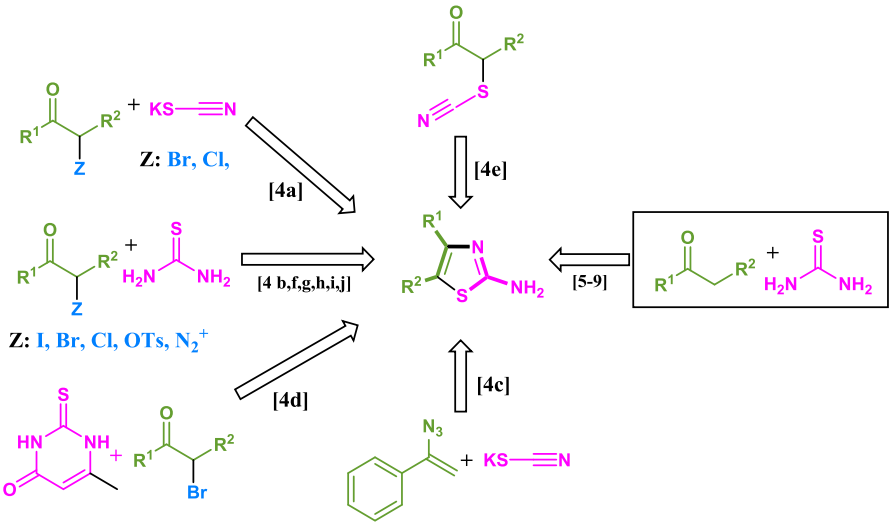


Fig. 1 Common methods for the synthesis of 2-aminothiazole

ketones has been well examined, but there is no reported information about aliphatic ketones as a substrate.

In recent years, different protocols have been introduced for the synthesis of 2-aminothiazole using methylcarbonyls and thiourea as substrates. Some of these methods include the following: $NaICl_2$, [20] O_2/KI/[Bmim]OTf, [21] and CBr_4/Et_3N, [22] and Fe_3O_4@SiO_2.TiO_2/NBS [23]. Despite the advantages of the previous methods, there is still a need to improve the synthesis of 2-aminothiazoles using new strategies and catalysts, due to the significant importance of the class of compounds in synthetic chemistry and pharmaceuticals.

Montmorillonite K10 (MMT-K10) is a layered aluminasilicate clay which has many applications in synthetic organic reactions [24–29]. The featured properties of montmorillonite are as follows: low cost, ease of handling, non-corrosiveness, suitable surface area (250 m^2/g), and reusability.

In continuation of previous workscarried out in our laboratory and in others, here we reveal MMT-K10 as an inexpensive, green and efficient catalyst in combination with iodine in the role of a reagent as a successful and efficient system for the synthesis of 2-aminothiazoles.

Experimental

General

All chemicals were purchased from Merck. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellets on a Shimadzu FT IR-8400S spectrometer. ^{1}HNMR (400 MHz) and

^{13}CNMR spectra were obtained using a Bruker DRX-400 AVANCE spectrometer. Analytical thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck) or neutral alumina oxide gel 60F 254 (Merck). Morphological characteristics of the nanostructures were characterized using a scanning electron microscope (SEM; EVO LS 10; Carl Zeiss, Germany) operating at an accelerating voltage of 20 kV under high vacuum.

Procedure for preparation of MMT-M^{n+}

A sample of 1 g MMT-K10 clay was stirred with 1 M metal nitrate (Al, Cu and Zn) solution for 3 days, filtered, and then washed with plenty of water to remove excess aluminium nitrate. The product was dried at 90 °C under vacuum tray drying for overnight [30].

Procedure for preparation of MMT-WCl_6

To a solution of montmorillonite K10 clay (2.7 g) in 50 mL of 2-propanol, 0.081 g of WCl_6 in 10 mL 2-propanol was added. The reaction mixture was stirred at room temperature for 4 h. Then, the propanol was removed under reduced pressure and the catalyst was dried in an oven at 110 °C for 3 h. The MMT-WCl_6 was obtained as a fine powder. The amount of tungsten loading was determined to be about 0.61 wt% [31].

Procedure for preparation of 2-aminothiazole by MMT-K10

A mixture of methylcarbonyl (0.5 mmol), thiourea (0.5 mmol), iodine (0.5 mmol), DMSO (2 mL) and 20 mg MMT-K10 was stirred at 80 °C. After completion of the reaction (monitored by TLC, petroleum:ethyl acetate, 4:1), the catalyst was separated by filtration, and then the solvent was removed under reduced pressure. The crude product was dissolved in hot water, extracted with ether (3 × 30 mL), and adjusted to pH = 9–10 by ammonia to give the solid products. Finally, the resulting precipitate was recrystallyzed by EtOH.

Thiazole-2-amine Pale yellow powder, m.p. = 89–90, Yield: 98 mg (98 %), IR (KBr): 3410, 3289, 3084, 1629, 1521, 1491, 698 (cm^{-1}), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.52 (*d*, *J* = 3.7 Hz, 1H), 6.75 (*s*, 2H, NH_2, D_2O exchangeable), 6.90 (*d*, *J* = 3.7 Hz, 1H), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.3, 138.1, 106.0., HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_3H_4N_2S$: 101.0173; found: 101.0178.

4-Phenylthiazol-2-amine Yellow crystal, m.p. = 151–153, Yield: 163 mg (93 %), IR (KBr): 3424, 3256, 2856, 1623, 1519, 1336, 728 (cm^{-1}), ^{1}H NMR (400 MHz, DMSO-d6): δ = 6.92 (*s*, 1H, thiazole), 7.22 (*s*, 2H, NH_2, D_2O exchangeable), 7.32 (*t*, *J* = 7.9 Hz, 1H, Ar–H), 7.69 (*t*, *J* = 7.9 Hz, 2H, Ar–H), 7.71 (*m*, *J* = 7.05 Hz, 2H, Ar–H), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.5, 151.1, 134.6, 128.6, 127.7, 126.0, 102.7, HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_9N_2S$: 177.0418; found: 177.0477.

4-(4-Nitrophenyl)thiazol-2-amine Yellow crystal, m.p. = 285–286, Yield: 212 mg (96 %), IR (KBr): 3400, 3115, 1626, 1596, 1507, 1331, 722 (cm^{-1}), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.45 (*s*, 1H, thiazole), 8.00 (*d*, *J* = 8.6 Hz, 2H,

Ar–H), 8.28 (*d*, $J = 8.6$ Hz, 2H, Ar–H), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 168.5, 147.8, 145.9, 140.8, 126.2, 124.0, 106.5$, HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_7ClN_2S$: 221.03; found 221.23.

4-(4-Chlorophenyl)thiazol-2-amine White crystal, m.p. = 160–162, Yield: 186 mg (89 %), IR (KBr): 3426, 2924, 1628, 1570, 1495, 744 (cm^{-1}), ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.24$ (*s*, 1H, thiazole, D_2O exchangeable), 7.55 (*d*, $J = 8.4$ Hz, 2H, Ar–H), 7.73 (*d*, $J = 8.4$ Hz, 2H, Ar–H), 8.43 (*s*, 2H, NH_2, D_2O exchangeable), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 169.2, 149.3, 134.4, 132.1, 129.0$ (2C), 127.8 (2C), 102.7, HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_7ClN_2S$: 211.0097; found 211.0092.

4-(3-Methylphenyl)thiazol-2-amine Yellow powder, m.p. = 88–91, Yield: 167 mg (88 %), IR (KBr): 3425, 2919, 1605, 1521, 1468, 714 (cm^{-1}), ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.48$ (*s*, 3H, CH3), 6.95 (*s*, 1H, thiazole), 7.02 (*s*, 2H, NH2), 7.05 (*d*, $J = 7.8$ Hz, 1H, Ar–H), 7.22 (*t*, 1H, $J = 7.9$ Hz, Ar–H), 7. 56 (*d*, $J = 7.9$ Hz, 1H, Ar–H), 7. 60 (*s*, 1H, Ar–H), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.6, 122, 123.4, 129, 130.4, 133, 137.7, 138.9, 169$, HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{10}N_2S$: 190.269; found: 191.0

4-(2-Hydroxyphenyl)thiazol-2-amine Yellow powder, m.p. = 138–139, Yield: 163 mg (85 %), IR (KBr): 3246, 2064, 1635, 1569, 1461, 743 (cm^{-1}), ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 6.88$ (*t*, 1H, $J = 7.6$ Hz, 1H, ArH), 6.89 (*d*, $J = 8.24$ Hz, 1H, ArH), 7.16 (*s*, 1H, thiazole, D2O exchangeable), 7.24 (*t*, $J = 8.24$ Hz, 1H, ArH), 7.52 (*d*, $J = 7.6$ Hz, 1H, ArH), 8.70 (*s*, 1H, OH, D_2O exchangeable), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 168.3, 155.5, 147.2, 128.9, 126.3, 118.9, 118.3, 116.9, 100.5$, HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_8N_2OS$: 193.0, found 193.1

4-(4-Hydroxyphenyl)thiazol-2-amine Yellow powder, m.p. = 198–200, Yield: 174 mg (91 %), IR (KBr): 3447, 2921, 1610, 1504, 1435, 834 (cm^{-1}), ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 6.69$ (*d*, $J = 8.5$ Hz, 2H, Ar–H), 6.70 (*s*, 1H, thiazole), 6.95 (*d*, 2H, NH2), 7.58 (*d*, $J = 8.5$ Hz, 2H, Ar–H), 9.50 (*s*, OH), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 168.3, 156.9, 149.9, 127.1, 126.3, 115.4, 98.8$, HRMS (ESI): *m/z* $[M + H]^+$ calcd for C9H9N2OS: 193.0430; found: 193.0427.

4-Methyl-5(ethoxycarbonyl)thiazol-2-amine White powder, m.p. = 177–179, Yield: 182 mg (98 %), IR (KBr): 3374, 3085, 1674, 1515, 1373, 756 (cm^{-1}), ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.21$ (*t*, $J = 7.1$, 3H, CH_3), 2.48 (*s*, 3H, CH_3), 4.12 (*q*, 2H, CH_2), 7.71 (S, 2H, NH_2), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 14.71, 17.45, 60.32, 107.90, 159.69, 162.47, 170.71$, HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_7H_{10}N_2O_2S$: 186.05; found: 186.23.

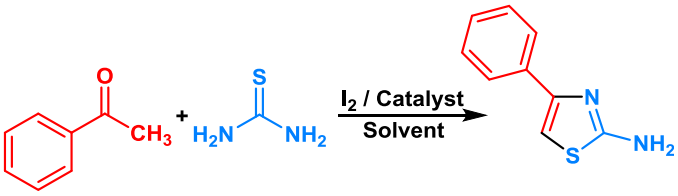
4-Methyl-5(methoxycarbonyl)thiazol-2-amine White powder, m.p. = 225–226, Yield: 170 mg (99 %), IR (KBr): 3374, 3085, 1682, 1644, 1504, 1320, 758 (cm^{-1}), ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.57$ (*s*, 3H, CH_3), 3.85 (*s*, 3H, CH_3), 6.12 (S, 2H, NH_2), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 15.4, 51.5, 116, 155.5, 166.5, 169.1$, HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_6H_8N_2O_2S$: 172.03; found: 172.20.

4-Methyl-5(allyloxycarbonyl)thiazol-2-amine White powder, m.p. = 148–149, Yield: 194 mg (98 %), IR (KBr): 3375, 3083, 1672, 1514, 1374, 754 (cm^{-1}), ^1H NMR (400 MHz, DMSO-d_6): $\delta = 2.38$ (*s*, 3H, CH_3), 4.15 (*d*, $J = 5.4$ Hz, 2H, CH_2), 5.26 (*d*, 1H, CH), 7.30 (*d*, 1H, CH), 5.92 (*m*, 1H, CH), 7.52 (*s*, 2H, NH_2), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 16.4$, 67, 116.11, 118.2, 132.1, 155.5, 166.5, 169.1, HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_6H_8N_2O_2S$: 198.5 found: 198.24.

Results and discussion

The reaction conditions were optimized for the synthesis of 2-aminothiazole using acetophenone and thiourea as model substrates and the obtained results are given in Table 1.

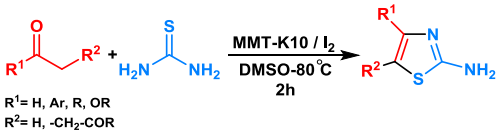
Table 1 Optimization of the reaction conditions



Entry	Catalyst (mg)	Solvent	Temperature (°C)	Yield (%)
1	–	EtOH	80	65
2	Bentonite (10)	EtOH	80	66
3	MMT-K10 (10)	EtOH	80	67
4	MMT-Al^{3+} (10) [30]	EtOH	80	55
5	MMT-Cu^{2+} (10) [30]	EtOH	80	50
6	MMT-Zn^{2+}(10) [30]	EtOH	80	50
7	MMT-WCl_6 (10)	EtOH	80	60
8	MMT-K10 (10)	DMSO	80	90
9	MMT-K10 (10)	CH_3CN	80	50
10	MMT-K10 (10)	EtOAc	80	35
11	MMT-K10 (10)	THF	80	40
12	MMT-K10 (10)	CH_3OH	80	35
13	MMT-K10 (10)	DMSO	90	85
14	MMT-K10 (10)	DMSO	70	80
15	MMT-K10 (5)	DMSO	80	85
16	MMT-K10 (20)	DMSO	80	96
17	MMT-K10 (30)	DMSO	80	94
18	MMT-K10 (40)	DMSO	80	92

Reaction condition: acetophenone (1 eq), thiourea (1 eq), iodine (1 eq), catalyst, and solvent stirred at 80 °C for 2 h

Table 2 MMT-K10 catalyzed synthesis of 2-aminothiazoles



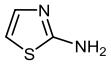
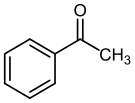
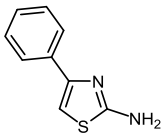
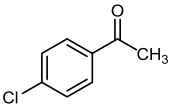
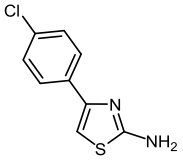
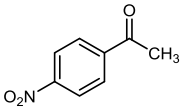
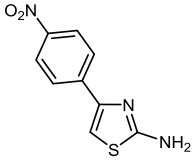
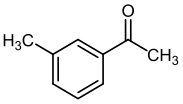
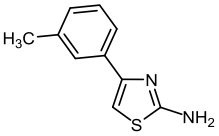
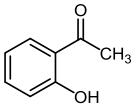
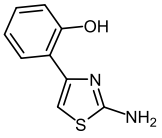
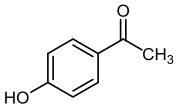
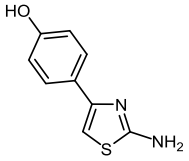
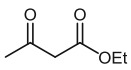
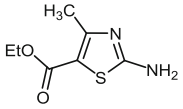
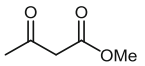
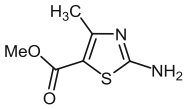
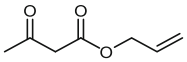
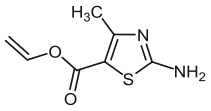
Entry	ketone	Product	Yield (%)
1			98
2			96
3			92
4			98
5			91
6			90
7			94

Table 2 continued

Entry	ketone	Product	Yield (%)
8			99
9			99
10			99

Reaction condition: acetophenone (0.5 mmol), thiourea (0.5 mmol), iodine (0.5 mmol), MMT-K10 (20 mg), and DMSO (2 mL) stirred at 80 °C for 2 h

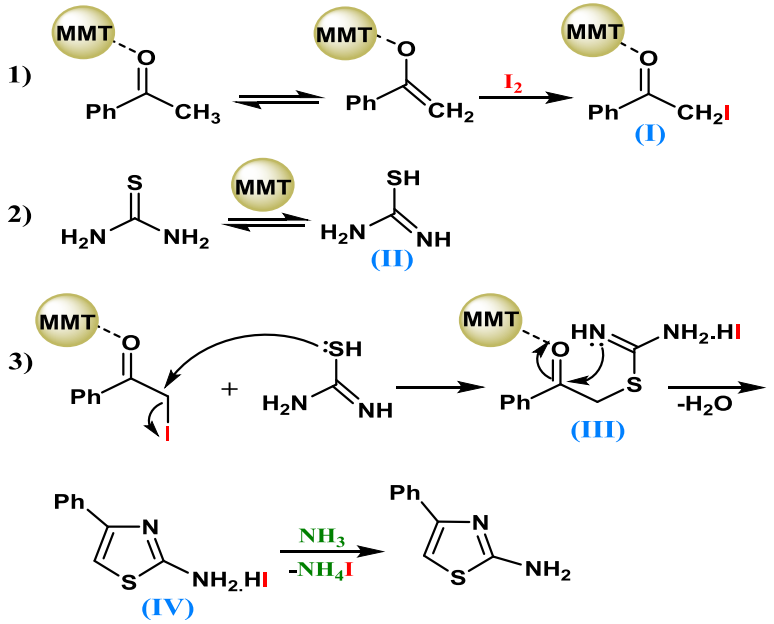
In the absence of the catalyst, 65 % of product was obtained at 80 °C in EtOH medium (Table 1, entry 1).

We screened various clays and modified clays as the catalyst, such as bentonite MMT-Al^{3+}, MMT-Cu^{2+}, MMT-Zn^{2+}, and MMT-WCl_6, to obtain the best catalyst for the synthesis of 2-aminothiazole. The best results were obtained for MMT-K10 [30]. The various solvents were examined and in the meantime dimethyl sulfoxide (DMSO) showed the best performance. Further, the temperature and the catalysis loading were evaluated at 80 °C and 20 mg, respectively, anf the optimized amount of the catalyst was chosen.

To develop the scope of the results, various methylcarbonyls as substrate were screened including methyl ketones, ketones, aldehydes, β-ketoesters, and diketone (Table 2).

The results showed that there are greater yields for more acidic substrates than for less acidic substrates. Ethyl acetoacetate, methyl acetoacetate, and allyl acetoacetate were almost entirely converted to the product (99 %). Acetaldehyde showed a very good yield (98 %) and the acetophenone derivatives displayed an acceptable performance (>90 %). Notably, 2-hydroxyacetophenone has the lowest performance because of steric hindrance and the electron donating of hydroxyl group (–OH).

Based on our previous understanding about the nature of the reaction mechanism and the structure of the catalyst, it is assumed that a-halo carbonyl species plays a key role in the reaction mechanism. [23]. Montmorillonite-K10 can act as a solid acid catalyst due to the existence of both Bronsted and Lewis acid sites. In the suggested mechanism, montmorillonite-K10 clay polarizes the carbonyl group of acetophenone and produces α-iodoacetophenone (I) (Scheme 1). Subsequently, a nucleophilic attack occurs in the α-position of the carbonyl group by



Scheme 1 Proposed mechanism for the synthesis of 2-aminothiazoles using MMT-K10

carbamimidothioic acid species (III). Finally, clay-promoted dehydrogenation gives 2-aminothiazoles (Scheme 1).

Conclusions

In summary, we have demonstrated a green and efficient protocol for the synthesis of 2-aminothiazoles using montmorillonite-K10 as the catalyst. We have used methylcarbonyl compounds and thiourea as raw materials. This method is convenient, highly efficient and avoids the use of expensive reagents, and catalysts.

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