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Eco-friendly synthesis of 2-aminothiazoles using Nafion-H as a recyclable catalyst in PEG–water solvent system

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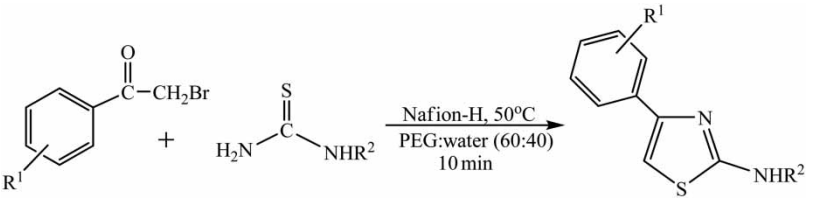
A simple, efficient, single step and environmentally benign synthesis of 2-aminothiazoles is described in this paper. This green protocol was catalyzed by recyclable solid supported Nafion-H using polyethylene glycol–water solvent system with improved efficiency and reduced waste production.



Keywords: 2-aminothiazoles; Nafion-H; polyethylene glycol; green; recyclable

1. Introduction

In the recent decades, one of the most challenging tasks for researchers is to achieve the most efficient methodology for the organic synthesis which can be realized by employing innovative research which comprehensively meets the requirement of atom economy, economy of steps and avoidance of any hazardous chemicals. One of the best methods will be that which will address the goals of green chemistry.

Thiazoles are known to be associated with diverse physiological activities. The thiazole framework, particularly 2-aminothiazole is an important medicinal scaffold. Several compounds possessing this framework are important ingredients in many pharmaceutical preparations used in the treatment of allergies (*1*), hypertension (*2*), inflammation (*3*), schizophrenia (*4*), bacterial (*5*) and HIV infections (*6*). Recently, it has been utilized for the treatment of pain (*7*), as fibrinogen receptor antagonists with antithrombotic activity (*8*), as inhibitors of bacterial DNA gyrase (*9*), and in the development of cyclin-dependent kinase inhibitors (*10*). So, the development of library

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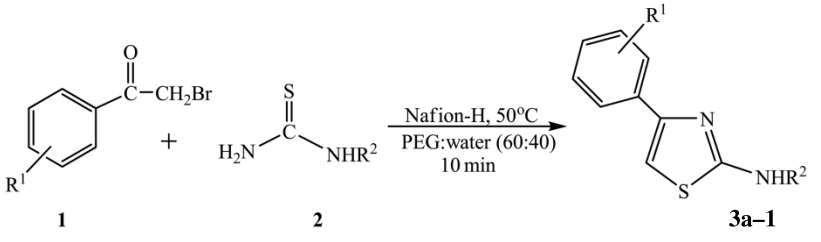
of 2-aminothiazoles might furnish additional lead molecules for the drug discovery. In view of the importance of 2-aminothiazoles and its derivatives, several methods have been reported for their synthesis in the literature (*11*). Some of these procedures have some major shortcomings such as low yield, high reaction temperatures, involvement of expensive, moisture and air-sensitive catalysts, tedious purification process and hazardous solvents. These processes also generate waste-containing solvent, catalysts, which have to be recovered, treated and disposed of. Despite this wide range of methods available, still there is a need to search for more better catalysts with regard to their toxicity, handling, availability, economic viability and operational simplicity.

Nafion-H, a perflourinated sulfonic acid resin, is a useful solid acid catalyst for a variety of acid-catalyzed organic transformations (*12*). It consists of a polymeric backbone with highly acidic sulfonic acid groups and possess hydrophobic ($-CF_2CF_2$) as well as hydrophilic regions ($-SO_3H$). The high catalytic activity of Nafion-H, its selectivity, recyclability, inertness, thermal stability and ease of separation from the reaction mixture render it a very attractive candidate (*13*). It has a catalytic activity comparable with that of Bronsted acids having $H_0 < -12$ (*13a*) (H_0 = Hammett acidity function). Owing to all these qualities, it has been found to be a suitable replacement for various homogeneous acid catalysts. Water and aqueous-based solvent systems may represent an increasingly significant choice for the replacement of traditional solvents in synthetic chemistry. A recent American Chemical Society Symposium volume highlighted some aspects of the use of water and aqueous solutions in green chemistry (*14*); however, relatively few articles have focused on the use of aqueous polyethylene glycol (PEG) solutions in organic reactions.

In this article, we describe the use of simple and widely available polymer PEG as a benign medium due to its low volatility, non-flammability, ease of work-up, ability to act as a phase-transfer catalyst and a good reaction medium, inexpensive price and eco-friendly nature (*15*). As a part of our ongoing research program to devise greener chemical transformations (*16*), we reveal herein for the first time a simple, convenient and an efficient method for the preparation of 2-aminothiazoles using Nafion-H as a catalyst coupled with aqueous PEG-400 system (Scheme 1).



Scheme 1. Synthesis of 2-aminothiazoles from α-bromoketones and thioureas.

2. Results and discussion

In an initial endeavor, a blank reaction was carried out using 1 equiv. each of phenacyl bromide and thiourea. These were stirred at ambient temperature in ethanol. After 3 h, only 65% of the expected product was obtained. The same reaction was then carried out using Nafion-H as a catalyst under similar conditions. Surprisingly, a significant improvement was observed and the yield was dramatically increased to 80% after stirring the mixture for only 20 min. To further improve the yield and to optimize the reaction conditions, the same reaction was carried out employing PEG as a solvent system. A remarkable improvement was observed and the yield

increased up to 92% after stirring the mixture for only 15 min. With these optimistic results in hand, we further investigated the best reaction conditions by using different ratios of PEG–water solvent system. A decrease in the quantity of PEG from 100% to 60% increased the product yield slightly from 92% to 96%. But a further decrease in the ratio of PEG decreased the product yield, which is attributed to the loss of solubility of the reactants.

The effect of different solvents on the reaction rate as well as yields of products was also examined (Table 1). Only acetonitrile afforded products in good yields with similar reaction times. The reason for the low yield in some solvents is due to the inability of solvent to swell Nafion-H which results in its low catalytic activities. Nafion-H being non-porous relies on the solvation of the ionic groups by an appropriate solvent to form solvents channels and clusters. The low yields are observed due to the failure of the substrate to be able to access the catalyst (*17*).

For practical applications of the catalyst Nafion-H, the lifetime of the catalyst and its reusability are important factors. The catalyst showed excellent recyclability in this reaction. The catalyst was physically removed by forceps after the completion of the reaction. The catalyst was washed with acetone, dried and reused as such for subsequent reactions (four runs) with fresh substrates under same conditions. The reaction times and yield remained the same, without the loss of catalytic activity (*18*). The catalyst still remained active after fourth run with 94% yield (Table 2).

Using the optimized conditions, the efficiency of this protocol was studied for the synthesis of various 2-aminothiazoles.Variety of thioureas (electron-donating, electron-withdrawing) exemplify the versatility of this protocol (Table 3).

A plausible mechanism for the synthesis of 2-aminothiazoles is shown in Scheme 2.

Table 1. Effect of solvent on the synthesis of 2-aminothiazole **3a**.[a]

Solvents	Time (min)	Yield (%)[b]
Ethanol	20	80
Acetonitrile	15	82
THF	25	76
Toluene	35	72
Ethylene glycol	25	82
PEG-400	15	92
PEG:H_2O		
90:10	10	96
80:20	10	96
70:30	10	96
60:40	10	96
50:50	15	88
40:60	25	83

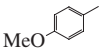
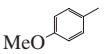
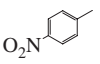
Notes: [a]Reaction conditions: phenacyl bromide (1 mmol), thiourea (1 mmol); catalyst: Nafion-H; temp.: 50 °C. [b]Isolated yields.

Table 2. Recycling yields.[a]

Number of cycles[a]	Fresh	Run 1	Run 2	Run 3	Run 4
Yield (%)[b]	96	96	96	96	94
Time (min)	10	10	10	10	10

Notes: [a]Reaction conditions: phenacyl bromide (1 mmol), thiourea (1 mmol); catalyst: Nafion-H; solvent: PEG:water (60:40) system; temp: 50 °C. [b]Isolated yields.

Table 3. Nafion-H-promoted synthesis of 2-aminothiazoles.[a]

Entry	R^1	R^2	Product	Time (min)	M.P. (°C)	Yield (%)[b]
1		−H	**3a**	10	114–118 (*19*)	96
2		−H	**3b**	15	126–128 (*19*)	96
3			**3c**	20	134–136 (*19*)	96
4			**3d**	10	164–166 (*19*)	97
5			**3e**	20	162–166 (*20*)	94
6			**3f**	8	174–176	96
7			**3g**	10	134–138 (*21*)	96
8			**3h**	15	160–164 (*22*)	96
9			**3i**	10	136–140	93
10			**3j**	10	110–116 (*23*)	96
11			**3k**	20	204–208 (*24*)	97
12			**3l**	25	206–210	97

Notes: [a]Reaction conditions: substituted phenacyl bromide (1 mmol), *N*-substituted thiourea (1 mmol); catalyst: Nafion-H; solvent: PEG:water (60:40) system; temp: 50 °C. [b]Isolated yields.

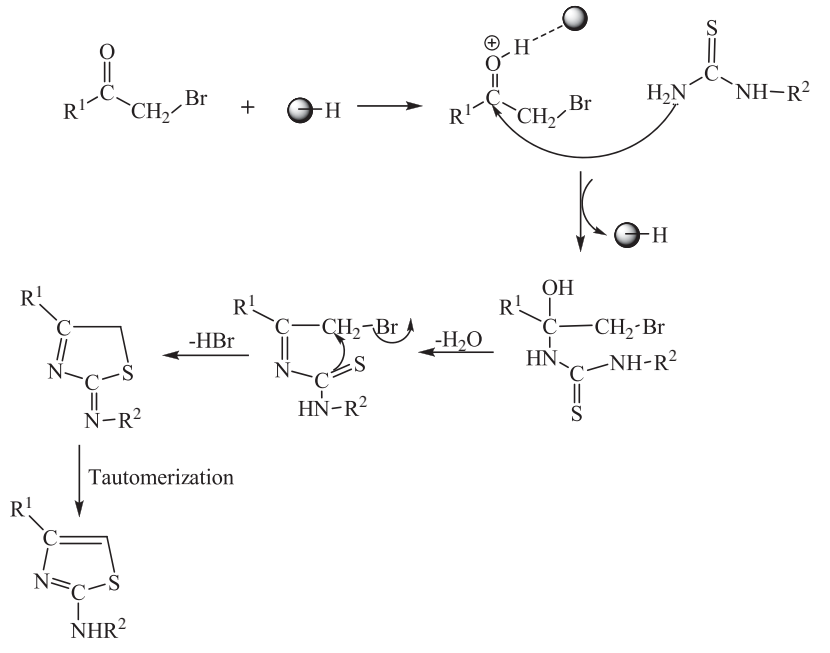
3. Conclusion

In summary, we have developed a new and highly efficient methodology for the synthesis of 2-aminothiazoles in the presence of catalytic amounts of Nafion-H employing PEG: water solvent system under very mild conditions. The simplicity/reuse of the catalyst due to its heterogeneous nature, excellent yields of the products and ease of work-up make this protocol an attractive, environmentally acceptable synthetic tool for the preparation of these substrates.

4. Experimental

4.1. *Materials and methods*

All chemicals were purchased from Sigma-Aldrich and were used as such. All reactions and purity of 2-aminothiazoles were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F_{254} plates (Merck) using 20% ethyl acetate and 80% petroleum



Scheme 2. Plausible mechanism for the Nafion-H catalyzed 2-aminothiazole synthesis.

ether as an eluent. The spots were detected either under UV light or by placing in an iodine chamber. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using KBr as pastilles. ^{1}H NMR and ^{13}C NMR were recorded on a JEOL JNM-ECX 400P FT NMR system using TMS as an internal standard. ESI-MS were recorded on waters LCT Micromass. Elemental analysis was performed on a Hereaus CHN rapid analyzer. The temperature of the reaction mixture was measured through a non-contact infrared minigun thermometer (AZ minigun type, model 8868).

4.2. *General procedure for the synthesis of 2-aminothiazoles*

A 50 ml round-bottomed flask was filled with phenacyl bromide (1 mmol), thiourea (1 mmol) and Nafion-H (1 bead) followed by 5 ml of PEG:water (60:40) solvent system. The mixture was then stirred at 50°C until the reaction was complete (TLC). Then to the reaction mixture, 50 ml of ice-cold water was added. The solid 2-aminothiazole product that separated out was filtered, then washed with water and dried. The crude product, thus obtained was subjected to purification by column chromatography on silica gel (100–200 mesh size) using 25% ethyl acetate in petroleum ether as an eluent to yield 2-aminothiazoles, **3a**–**l**. The structures of all products were unambiguously established on the basis of spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, elemental analysis) and melting point determination (*19–24*).

4.3. *Regeneration of catalyst*

The catalyst was washed successively with acetone and deionized water and then dried overnight at 105°C. The obtained catalyst had the same catalytic activity as the fresh catalyst.

4.4. *Spectral data for the synthesized 2-aminothiazole derivatives*

4.4.1. *2-Amino-4-phenyl thiazole (**3a**)*

White solid. IR (KBr) ν_{max} cm^{-1}: 3369, 3255, 1624, 1462, 1377, 769, 689. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 6.96$ (s, 1H, −CH), 8.34 (br s, 2H, NH_2), 7.35–7.58 (m, 5H, Ar-H).^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 101.74, 125.43, 128.07, 128.66, 129.22, 138.75, 170.17$. m/z (ESI-MS, HRMS): 176.332 (M^+). $C_9H_8N_2S$: Calcd. C, 61.33; H, 4.57; N, 15.8; found C, 61.24; H, 4.61; N, 15.7.

4.4.2. *2-Amino-4-(4′-methylphenyl) thiazole (**3b**)*

Creamy white solid. IR (KBr) ν_{max} cm^{-1}: 3383, 3264, 1627, 1570, 1377, 765, 653. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 6.81$ (s, 1H, −CH), 8.87 (br s, 2H, NH_2), 2.31 (s, 3H, Me), 7.18–7.48 (m, 4H, Ar-H).^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 20.49, 99.09, 124.30, 124.79, 129.03, 138.24, 139.20, 169.82$. m/z (ESI-MS, HRMS): 190.549 (M^+). $C_{10}H_{10}N_2S$: Calcd. C, 63.10; H, 5.3; N, 14.7; found C, 63.30; H, 5.12; N, 13.93.

4.4.3. *2-Phenylamino-4-phenyl thiazole (**3c**)*

White solid. IR (KBr) ν_{max} cm^{-1}: 3256, 1602, 1542, 1444, 1246, 750, 706. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.76$ (s, 1H, -CH), 8.18 (br s, 1H, NH), 6.99-7.82 (m, 10H, Ar-H).^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 101.54, 118.29, 122.99, 126.09, 127.90, 128.60, 129.34, 134.26, 140.18, 150.89, 164.98$. m/z(ESI-MS, HRMS): 252.598 (M^+). $C_{15}H_{12}N_2S$: Calcd. C, 71.3; H, 4.8; N, 11.1; found C, 71.1; H, 5.01; N, 10.95.

4.4.4. *2-Phenylamino-4(4′-methylphenyl) thiazole (**3d**)*

Light yellow solid. IR (KBr) ν_{max} cm^{-1}: 3246, 1599, 1462, 1326, 751, 692. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.66$ (s, 1H, −CH), 8.59 (br s, 1H, NH), 2.36 (s, 3H, Me), 7.38–7.70 (m, 9H, Ar-H).^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 21.29, 99.12, 119.50, 125.10, 125.80, 129.75, 139.33, 160.03$. m/z (ESI-MS, HRMS): 266.878 (M^+). $C_{16}H_{14}N_2S$: Calcd. C, 72.10; H, 5.3; N, 10.6; found C, 72.28; H, 5.12; N, 10.24.

4.4.5. *2-(1′-Naphthyl)-amino-4-phenyl thiazole (**3e**)*

White solid. IR (KBr) ν_{max} cm^{-1}: 3179, 1560, 1420, 1396, 771, 708. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.77$ (s, 1H, −CH), 1.88 (br s, 1H, NH), 7.29−7.90 (m, 12H, Ar-H).^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 101.97, 118.55, 121.24, 125.64, 125.83, 126.01, 126.52, 127.86, 128.61, 134.51, 136.09, 152.76, 167.92$. m/z (ESI-MS, HRMS): 302.089 (M^+). $C_{19}H_{14}N_2S$: Calcd. C, 75.47; H, 4.67; N, 9.26; found C, 75.23; H, 4.78; N, 9.11.

4.4.6. *2-(1′-Naphthyl)-amino-4(4″-bromophenyl) thiazole (**3f**)*

White solid. IR (KBr) ν_{max} cm^{-1}: 3054, 1544, 1397, 1105, 767, 680. ^{1}H NMR (DMSO-d_6, 400 MHz,): $\delta = 7.02$ (s, 1H, −CH), 10.14 (br s, 1H, −NH), 7.45−7.74 (m, 11H, Ar-H).^{13}C NMR (DMSO-d_6, 75 MHz,): 102.84, 121.80, 123.87, 125.41, 125.56, 125.81, 127.25, 127.89, 131.13, 146.76, 166.50. m/z (ESI-MS, HRMS): 379.965 (M^+). $C_9H_{13}BrN_2S$: Calcd. C, 59.85; H, 3.44; N, 7.35; found C, 59.67; H, 3.27; N, 7.22.

4.4.7. *2-(4′-Bromophenyl)-amino-4-phenyl thiazole (**3g**)*

Light brown solid. IR (KBr) ν_{max} cm^{-1}: 3379, 1560, 1326, 818, 770, 706, 672. ^1H NMR (DMSO-d_6, 400 MHz,): $\delta = 7.09$ (s, 1H, −CH), 8.06 (br s, 1H, −NH), 7.36−7.86 (m, 11H, Ar-H).^{13}C NMR (DMSO-d_6,75 MHz,): 102.13, 115.06, 119.54, 126.07, 126.45, 128.03, 128.66, 132.29, 134.24, 139.24, 151.75, 163.70. m/z (ESI-MS, HRMS): 329.275 (M^+). $C_{15}H_{11}BrN_2S$: Calcd. C, 54.39; H, 3.55; N, 8.46; found C, 54.20; H, 3.27; N, 8.22.

4.4.8. *2-(4′-Methoxyphenyl)-amino-4-phenyl thiazole (**3h**)*

White solid. IR (KBr) ν_{max} cm^{-1}: 3383, 1565, 1305, 1245, 827, 768, 705. ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 6.75$ (s, 1H, −CH), 1.74 (s, 3H, OMe), 1.74 (br s, 1H, −NH), 6.91-7.83 (m, 9H, Ar-H).^{13}C NMR (DMSO-d_6,75 MHz,): 55.49, 101.14, 114.61, 122.08, 126.05, 127.73, 128.52, 133.64, 134.59, 151.31, 156.28, 167.18. m/z (ESI-MS, HRMS): 282.564 (M^+). $C_{16}H_{14}N_2OS$: Calcd. C, 68.06; H, 5.00; N, 9.92; found C, 67.88; H, 4.84; N, 9.67.

4.4.9. *2-(4′-Methoxyphenyl)-amino-4(4″-methylphenyl) thiazole (**3i**)*

Yellow solid. IR (KBr) ν_{max} cm^{-1}: 3383, 1592, 1482, 1388, 769, 671. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 3.82$ (s, 3H, OMe), 2.37 (s, 3H, Me), 6.69 (s, 1H, −CH), 1.73 (s, 1H, −NH), 6.90–7.72 (m, 8H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 21.29$, 55.53, 98.87, 114.96, 122.94, 125.79, 128.36, 129.67, 131.68, 139.10, 146.51, 157.57, 167.99. m/z (ESI-MS, HRMS): 296.102 (M^+). $C_{17}H_{16}N_2OS$: calcd. C, 68.89; H, 5.44; N, 9.45; found C, 68.73; H, 5.31; N, 9.34.

4.4.10. *2-(4′-Methylphenyl)-amino-4-phenylthiazole (**3j**)*

White solid. IR (KBr) ν_{max} cm^{-1}: 3245, 1610, 1545, 1509, 1465, 1247, 824, 752, 669. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.33$ (s, 3H, Me), 6.79 (s, 1H, −CH), 6.69 (br s, 1H, −NH), 7.30–7.84 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 20.78$, 101.44, 118.91, 126.06, 127.80, 128.58, 129.94, 132.95, 134.55, 137.80, 151.19, 165.47.m/z (ESI-MS, HRMS): 266.444 (M^+). $C_{16}H_{14}N_2S$: Calcd. C, 72.15; H, 5.30; N, 10.52; found C, 71.89; H, 5.09; N, 10.22.

4.4.11. *2-(4′-Hydroxyphenyl)-amino-4-phenylthiazole (**3k**)*

White solid. IR (KBr) ν_{max} cm^{-1}: 3322, 2917, 1542, 1436, 1244, 820, 750, 663. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 6.74$ (s, 1H, −CH), 8.61 (br s, 1H, −NH), 6.83–7.86 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 101.95$, 116.53, 121.76, 126.83, 128.45, 129.34, 134.68, 135.90, 151.80, 167.66. m/z (ESI-MS, HRMS): 266.444 (M^+). $C_{15}H_{12}N_2OS$: Calcd. C, 67.14; H, 4.51; N, 10.44; found C, 6728; H, 4.32; N, 10.27.

4.4.12. *2-(4′-Nitrophenyl)-amino-4-phenylthiazole (**3l**)*

Orange solid. IR (KBr) ν_{max} cm^{-1}: 3302, 2922, 1533, 1306, 1264, 1180. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 6.99$ (s, 1H, −CH), 10.47 (br s, 1H, −NH), 7.39-8.22 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 103.21$, 115.84, 124.98, 125.57, 127.52, 128.25, 134.01, 140.29, 146.76, 151.01, 161.65. m/z (ESI-MS, HRMS): 297.062 (M^+). $C_{15}H_{11}N_3O_2S$: Calcd. C, 60.59; H, 3.73; N, 14.13; found C, 60.45; H, 3.62; N, 14.23.

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