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Article

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Thiocyanation and 2-amino-1,3-thiazole formation in water using recoverable and reusable glycosylated resorcin[4]arene cavitands

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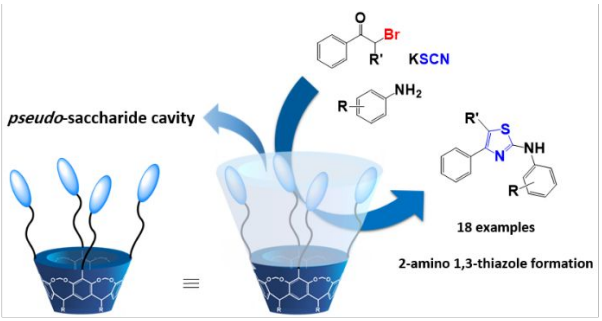
Supporting Information Placeholder



ABSTRACT: A family of three spatially directional resorcin[4]arene cavitand glycoconjugates (**RCGs**) have been applied as efficient recoverable and reusable inverse phase transfer catalysts for *eco*- and environmentally friendly thiocyanation and 2-amino-1,3-thiazole formation reactions in water. The results show that **RCGs** (1 mol%) were capable to host and catalyze various water-insoluble bromo/thiocyanato substrates in water without the use of any co-organic solvents. The recoverability and reusability of **RCG** catalytic systems, i.e., **RCG1** and **RCG3**, were also examined upon a simple extraction of the desired products using DCM or ethyl acetate, followed by subjecting the recovered aqueous solution containing the **RCG** catalysts for the next reaction cycles.

INTRODUCTION

1,3-thiazole ring, among heterocyclic ring systems, is uniquely important because of its presence in many natural products and biomolecules possessing wide range of pharmacological activities. Biological importance of thiazoles has led this ring system to be explored as a suitable heterocyclic core in design and development of novel therapeutic agents.[1] Structural modifications around the thiazole ring has been exploited for its role as an important pharmacophore in many clinically used drugs.[2] Among different synthetic derivatives of 1,3-thiazoles, 2-amino-1,3-thiazoles are an attractive moiety in medicinal chemistry with a wide spectrum of biological activities.[2-3] Many marketed drugs, such as abafungin (antifungal agent) nitazoxanide (antiparasitic agent), meloxicam (anti-inflammatory agent), and dasatinib (antineoplastic agent) contain the 2-amino thiazole heterocyclic core (Figure 1).

The Hantzsch reaction, which uses α-halocarbonyl compounds to couple with thioureas or thioamides, has been one of the widely used methods for the synthesis of 2-aminothiazoles.[4] Reactions directly starting from ketones, phenyl acetylene or styrene with thioureas have been also reported for synthesis of 2-aminothiazole substrates.[5] As well, modified version of the Hantzsch thiazole synthesis has been reported by α-halogenated ketones with amines in the presence of potassium thiocyanate salt.[6] All of these reactions were carried out in hazardous organic solvents, suffer from harsh reaction conditions, poor functional group tolerance, limited starting materials and involve tedious workup because of the reagents used. Considering the importance of the 2-aminothiazole heterocyclic core, it is desirable and challenging to develop efficient and green catalyst along with new routes for the construction of such thiazole moiety. Incidentally, β-cyclodextrin (β-CD),[7] lipase[8] (biocatalyst) and Cu(I)-catalyst,[9] have also been utilized in the synthesis of thiazole heterocycles.

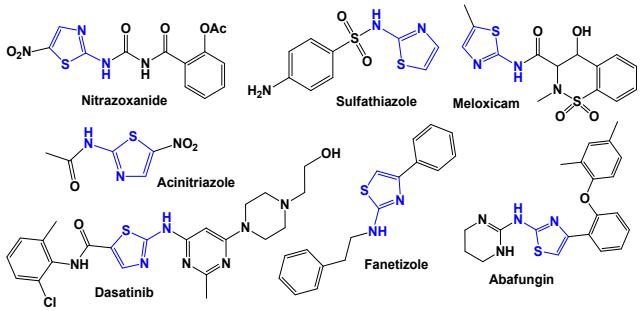


Figure 1. A few marketed 2-amino-1,3-thiazole drugs.

In recent years, we have developed a new catalytic systems based on the spatial directionality of the resorcin[4]arene cavitand glycoconjugates (**RCGs**)[10] (Figure 2). The multiple β-D-glucopyranose units on the cavitand rigid cores remarkably provide a "*pseudo*-saccharide" cavity, which we have found is able to host a variety of organic guests and catalyze chemical reactions in water. Similar to the cyclodextrin, the **RCGs** are efficient catalysts in various organic reactions in water, namely; thiocyanation, 2-amino-1,3-thiazole formation, Cu(I)-catalyzed azide-alkyne coupling (CuAAC) and impart stereoselectivity in one-pot three-components Mannich-type reactions (Figure 3).[10a] Also, we have recently reported on the formation of 1,4-disubstituted 1,2,3-triazoles in water catalyzed by octavalent resorcin[4]arene glycoconjugate **RG**.[10b]

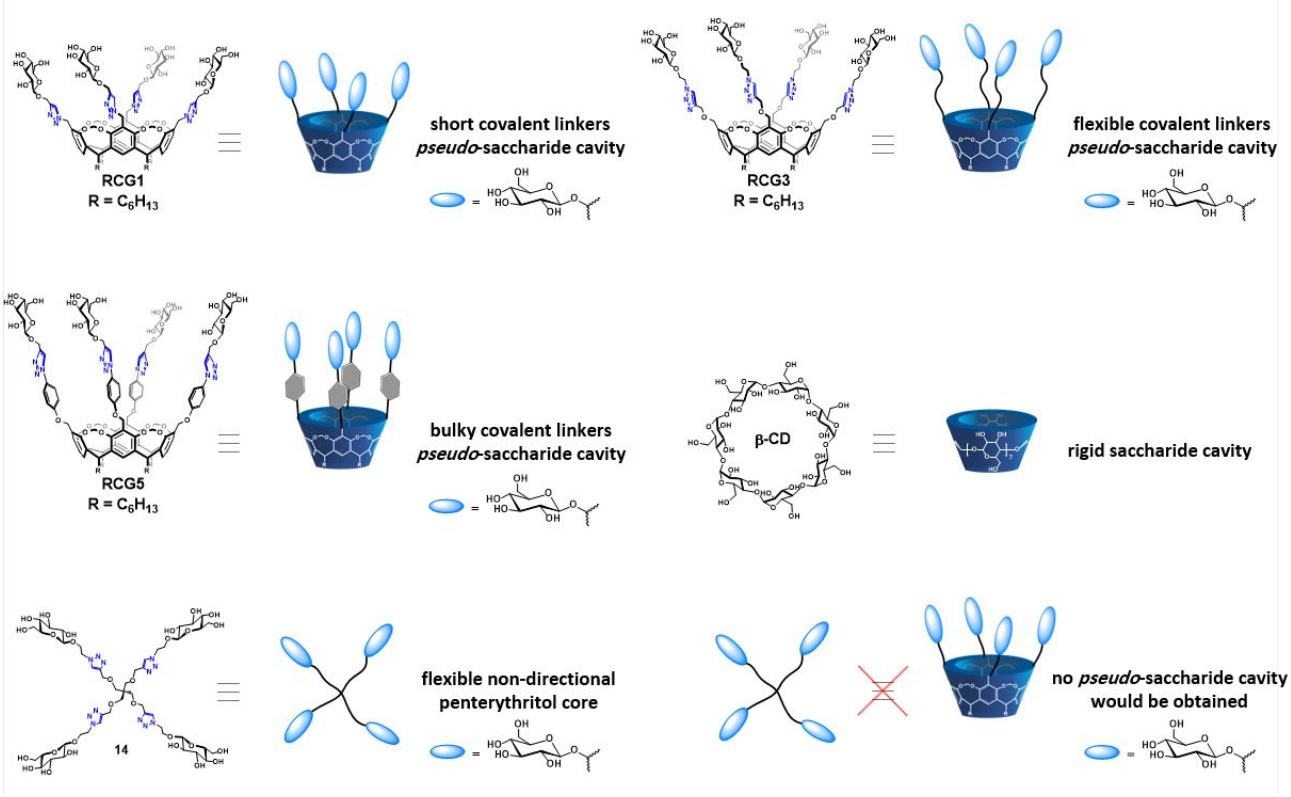


Figure 2. Structures of **RCGs**, β-CD and compound **14**.[10a]

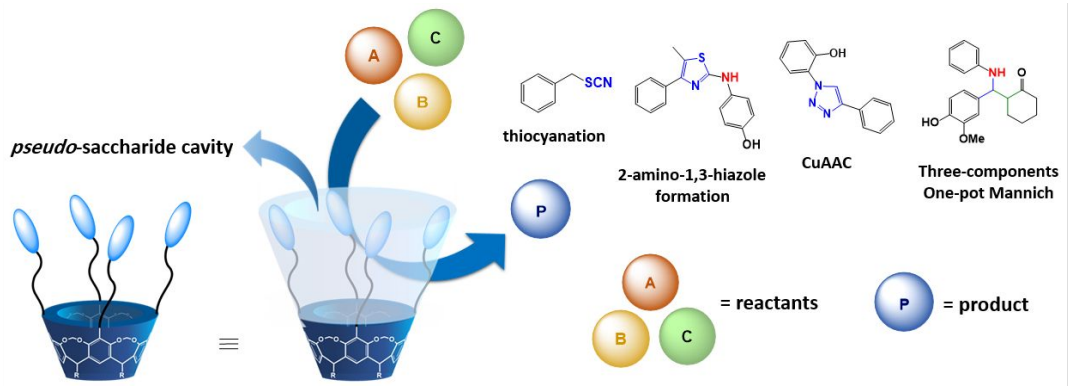


Figure 3. Different organic transformations catalyzed by **RCG3** in water.[10a]

In this manuscript, we focus our interest extending the thiocyanation and 2-amino-1,3-thiazole formation in water using **RCGs**. In here, β-cyclodextrin (β-CD) and compound **14**[10a] that is composed of a flexible "non-directional" pentaerythritol core which lacks the rigidity and spatial directionality were used for comparison (Figure 2). While **RCG1** is composed of short saccharide covalent linkers on its upper rim, **RCG3** and **RCG5** consist of more flexible and bulkier covalent spacers, respectively, on their macrocyclic upper cores (Figure 2).

RESULTS AND DISCUSSION

Molecules containing thiocyanate moieties have received a great interest in the field of organosulfur chemistry.[11] They are known to have insecticidal[12] and biocidal[13] activities and are found in some anticancer natural products derived from cruciferous vegetables.[14] Also, thiocyanates are used as a key-

intermediate in various organic transformations,[15] especially, the α-thiocyanato carbonyl containing ketones which are applied as starting materials in the synthesis of 2-amino-1,3-thiazole substrates. Considering the thermally instability of the thiocyanate ion and its tendency to rearrange to isothiocyanate,[16] number of methods have been sought to develop new strategies to achieve the thiocyanate substrates in quantitative yields by using phase transfer catalysts (PTCs),[17] microwave assistance,[18] or ionic liquids (ILs).[19]

Accordingly, we investigated the thiocyanate formation in water catalyzed by **RCGs**, β-CD and model compound **14**. Figure 4 summarizes optimization process for the thiocyanation reaction of benzyl bromide (1.0 mmol) with potassium thiocyanate (1.1 equiv.) in 10 mL of water. Duplicate reactions were performed in the presence or in the absence of the added catalysts (1 mol%) only in 5 min at different temperatures, i.e., 25, 50, 80 ^{0}C (Figure 4).

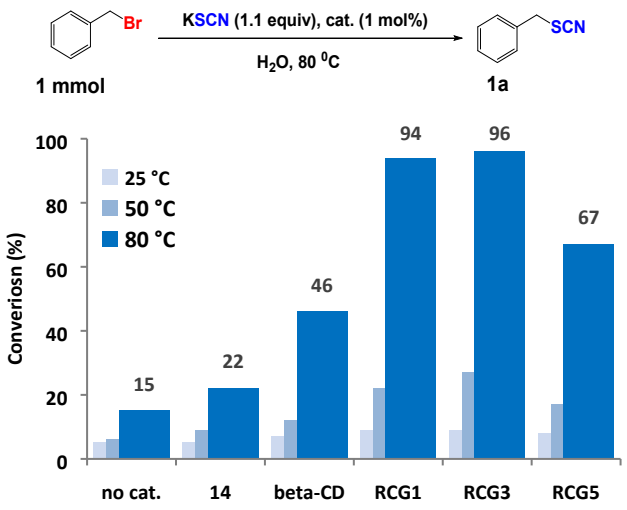


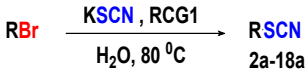
Figure 4. Conversion (%) of benzyl thiocyanate **1a** at 80 ^{0}C with/without the additive catalysts.

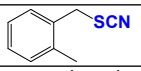
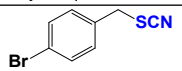
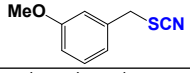
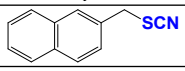
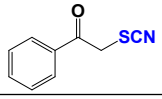
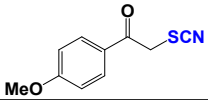
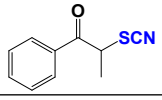
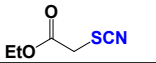
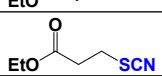
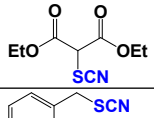
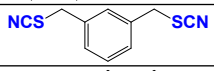
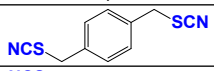
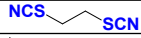
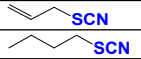
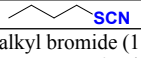
From the results in Figure 4, it was observed that thiocyanation proceeded poorly at 25 ^{0}C with/without the added catalysts (<10% conv.). Although, raising the temperature to 50 ^{0}C showed a slight improvement but yields were still less than 20%. At a higher reaction temperature, i.e., 80 ^{0}C, much higher yields were observed in the presence of the added catalysts. Notably, in the reaction catalyzed by **RCG1** and **RCG3** at 80 ^{0}C, nearly quantitative yield of 94% and 96%, respectively, of benzyl thiocyanate **1a** was observed. While 46%, 22% and 15% yields were obtained for reactions catalyzed by β-CD, compound **14** and blank (no added catalyst), respectively.

Significantly, among the **RCG** catalysts tested, **RCG1**/**RCG3** were preferred compared to the **RCG5** (67% yield) suggesting that the nature of the covalent linkers, i.e.; flexibility and steric hindrance, has a major influence on the construction of *pseudo*-saccharide cavity and thus on their catalytic efficiencies. Also, the results revealed **RCGs** to be more efficient catalysts than β-CD (rigid saccharide macrocycle) in facilitating the thiocyanation of benzyl bromide in water. The lack of significant catalytic activity in the reaction with the added non-directional glyco-pentaerythritol **14** suggested the importance of spatial directionality provided by the cavitand rigid core in facilitating the formation of the *pseudo*-saccharide cavity for catalysis.

Owing to the observed catalytic efficiencies of **RCG1** and **RCG3** in catalyzing the thiocyanation reaction of benzyl bromide in water, we further investigated their performance in thiocyanations of various alkyl/aryl halides and thiazole formation reaction along with their catalytic reusability studies. For example, in Table 1, we summarized the thiocyanation reactions for various hydrophobic alkyl and aryl bromides in water using **RCG1** catalyst.

Table 1. Synthesis of alkyl/aryl thiocyanate using **RCG1**.[a]



Entry	Product	Structure	Time (min)	Conv. (%)[b]
1	**2a**		30	91
2	**3a**		30	92
3	**4a**		30	98
4	**5a**		60	97
5	**6a**		30	96
6	**7a**		35	99
7	**8a**		35	95
8	**9a**		20	96
9	**10a**		30	98
10	**11a**		35	99
11	**12a**		25	93
12	**13a**		50	96
13	**14a**		40	92
14	**15a**		45	95
15	**16a**		40	83
16	**17a**		15	85
17	**18a**		45	98

[a]Reaction condition: aryl/alkyl bromide (1.0 mmol), KSCN (1.1 mmol) and **RCG1** (1 mol%), H_2O (10 mL), 80 ^{0}C, [b]Determined by ^{1}H-NMR for the crude reaction mixture after extraction with DCM.

It was evident from the results that a variety of water-insoluble alkyl/benzyl bromide derivatives were well tolerated in water and within 30 minutes more than 90% product yields were observed. The catalyst was tolerant of cyclic/acylic and aromatics along with different functionalities, including unsaturation, carbonyl containing ester and ketone functionalities.

The recoverability and reusability of **RCG1** was investigated for the thiocyanation reaction. In the reaction of benzyl bromide catalyzed by **RCG1**, after extracting the formed benzyl thiocyanate **1a** with DCM, the recovered aqueous phase containing **RCG1** was subjected to the next thiocyanation reaction cycle to evaluate its residual catalytic efficiency (Figure 5). Most impressively, **RCG1** catalyst retained most of its catalytic activity over five extraction and catalytic cycles resulting in >80% yield of the benzyl thiocyanate **1a**. Such result indicates that **RCG1** can be practically recovered and reused.

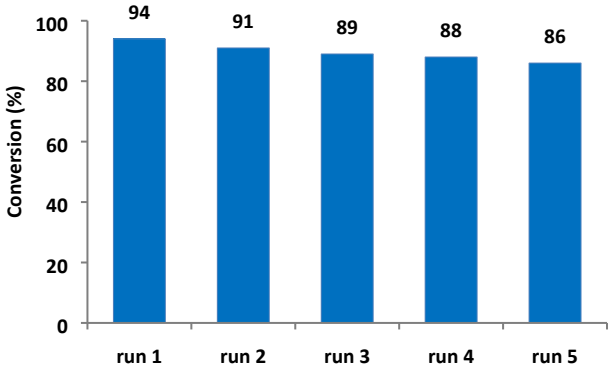


Figure 5. Reusability of **RCG1** for thiocyanation of benzyl bromide in water.

Since thiocyanates are a key-intermediate (starting material) in the synthesis of thiazoles, the condensation of α-thiocyanato ketone with aniline in water was investigated (Figure 6) for the synthesis of 2-aminothiazole **1b**. The reaction between α-thiocyanato propiophenone (1.0 mmol) and aniline (1.1 mmol) with/without the additive catalysts (1 mol%, **RCGs**, β-CD and model compound **14**) were carried out in 10 mL of water at 80 ^{0}C in 1 hr and results are shown in Figure 6.

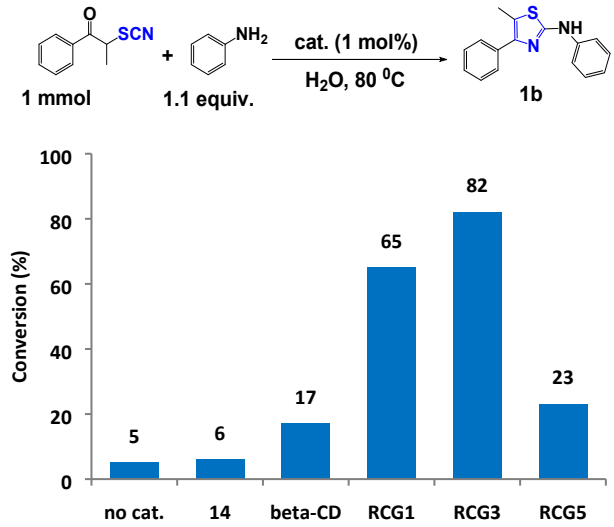
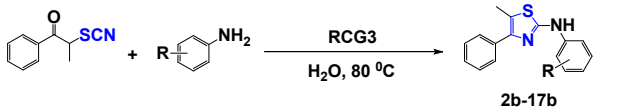


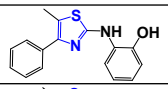
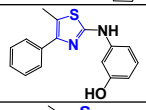
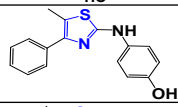
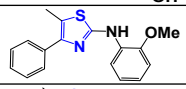
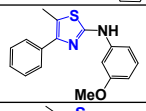
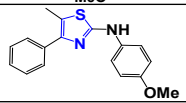
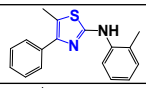
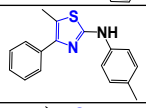
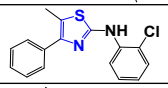
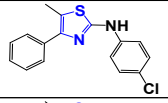
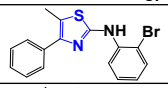
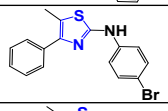
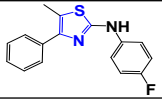
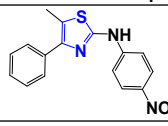
Figure 6. Conversion (%) of thiazole **1b** at 80 ^{0}C with/without the additive catalysts.

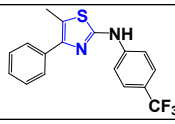
Like observations made during the thiocyanation reaction, poor conversions (<17%) were observed with compound **14**, β-CD or in absence of an additive catalyst. Expectedly, **RCG1** and **RCG3** led to highest conversions of 65% and 82%, respectively. Noticeably again, the catalytic efficiency was different among the **RCGs** (only 23% when **RCG5** was applied) suggesting a definite role for the spatial directionality imparted by the cavitand core along with the covalent linkers between the cavitand and the glycoside units in the formation of the *pseudo*-saccharide bucket site required for catalysis.

RCG3 robustness in catalyzing the formation of 2-aminothiazole in water upon the reaction of α-thiocyanato propiophenone (1.0 mmol) with a variety of substituted aniline derivatives (1.1 equiv.) was evaluated (Table 2).

Table 2. Scoping the thiazole formation using **RCG3**.[a]



Entry	Product	Structure	Conv. (%)[b]
1	**2b**		98
2	**3b**		97
3	**4b**		98
4	**5b**		97
5	**6b**		96
6	**7b**		98
7	**8b**		98
8	**9b**		99
9	**10b**		23
10	**11b**		35
11	**12b**		28
12	**13b**		31
13	**14b**		88
14	**15b**		N/A

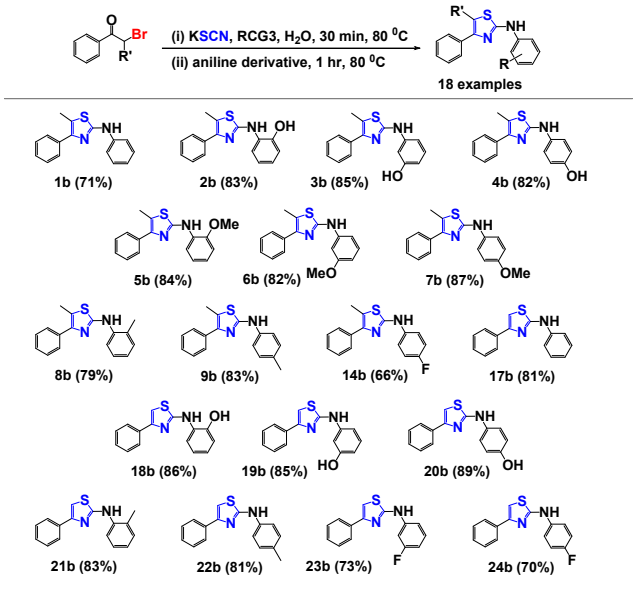
15	**16b**		N/A

[a]Reaction condition: **8a** (1.0 mmol), aniline derivatives (1.1 mmol) and **RCG3** (1 mol%), H_2O (10 mL), 1 hr, 80 ^{0}C, [b]Conv. (%) for the crude reaction mixture after extraction with ethyl acetate.

From the results, it was observed that the condensation occurred with ease and with excellent yields (>95% conv.) when electron-donor substituted anilines (entries 1-8) were used. However, halogenated aniline gave lower yields (23-35%, entries 9-12) with exception of 4-fluoroaniline which gave 88% conversion (entry 13). The strongly electron withdrawing, i.e., 4-nitro- and 4-trifluoromethylaniline, were found to be unreactive (entries 14 & 15).

Since, the **RCGs** can effectively catalyze the thiocyanation and thiazole formation, it was logical to extend their catalytic capability to a one-pot three component coupling reaction for the formation of 2-aminothiazoles (Scheme 1). The one-pot reaction essentially is a combination of two artificial synthetic steps; (i) formation of α-thiocyanato carbonyl containing ketones within 30 minutes at 80 ^{0}C, followed by (ii) direct addition of aniline derivatives on the reaction mixture at 80 ^{0}C for the synthesis of the targeted 2-aminothiazole compounds (Figure 7). It was observed from all reactions that **RCG3** successfully catalyzed the one-pot thiazole formation in water of various 2-amino-1,3-thiazoles in good to high yield, i.e., 66-87 %, Scheme 1.

Scheme 1. One-pot thiocyanation/thiazole formation using **RCG3**



[a]Reaction condition: (i) alpha-bromo propiophenone (1.0 mmol), KSCN (1.1 mmol), H_2O (10 mL), 30 min, 80 ^{0}C; (ii) aniline derivatives (1.1 mmol) and **RCG3** (1 mol%), H_2O (10 mL), 1 hr, 80 ^{0}C, [b]Isolated yield.

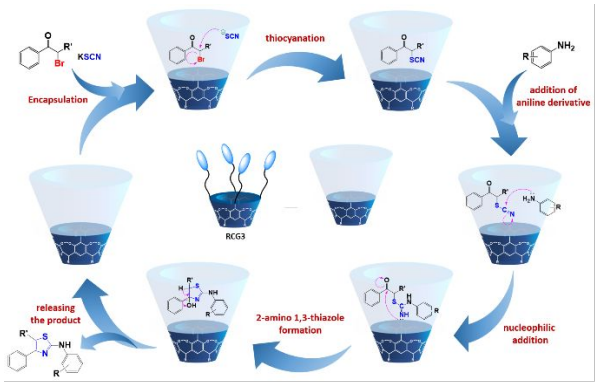


Figure 7. Proposed reaction mechanism for the one-pot thiazole formation in water catalysed by **RCG3**.

Moreover, we also examined the recoverability and reusability of **RCG3**, after extraction of formed 2-aminothiazole product **1b** with ethyl acetate, the aqueous phase containing **RCG3** catalyst was recovered (Figure 8). The aqueous solution was then directly subjected without further purification for the next thiazole formation reaction cycle to evaluate its residual catalytic efficiency, which was significantly maintained for five extraction/reaction cycles (>65%, Figure 8).

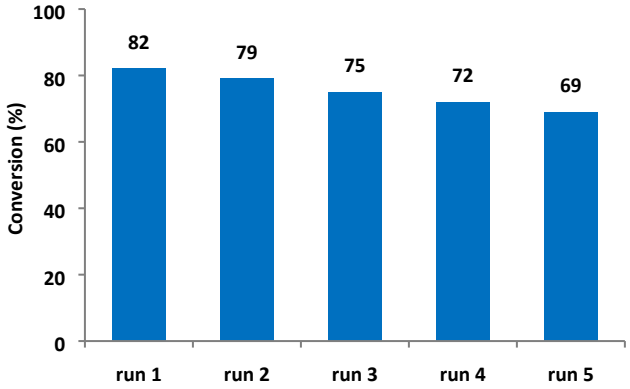


Figure 8. Reusability of **RCG3** for thiazole formation of α-thiocyanato propiophenone in water.

In conclusion, resorcin[4]arene cavitand glycoconjugates (**RCGs**) were found to be excellent, recoverable and reusable inverse phase transfer catalysts in thiocyanation and 2-amino-1,3-thiazole formation reactions in aqueous condition. Such method can be substantially practicable in a green approach for the synthesis of thiocyanate and thiazole species in an ideal reaction medium, water. **RCGs** were found to have several advantages, including low catalytic loading (1 mol%), *eco*-friendly aqueous reaction condition, significantly shorter reaction time, recyclability, and reusability along with high yield desired products.

EXPERIMENTAL SECTION

General

^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-250 and Inova 400 spectrometers. Sample concentrations were about 10 % (w/v) in $CDCl_3$ and DMSO-d_6 and the *J* values are given in Hz. The mass spectral analyses were performed on an Aligent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS.

Materials

All reagents were used with no further purification unless otherwise specified. 2-, 3- 4-amino phenols and 4-anisidine were re-crystallized out from (3:7) ethyl acetate/hexane solvents.

General procedure for the synthesis of resocrcin[4]arene cavitands glycoconjugates (RCGs**).** All glycosylated resorcin[4]arene cavitands were prepared following the typical procedure reported previously.[10a]

Resorcin[4]arene Cavitand Glycoconjugate 1 (RCG1).[10a] Pale yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (s, 4H), 7.67 (s, 4H), 5.99 (d, *J* = 7.0 Hz, 4H), 5.31 (s, 8H), 4.84 (d, *J* = 12.11 Hz, 4H), 4.61 (d, *J* = 12.11 Hz, 4H), 4.61 (t, *J* = 8.1 Hz, 4H), 4.26 (d, *J* = 7.7 Hz, 8H), 3.71 (d, *J* = 10.3 Hz, 4H), 3.48 (dd, *J* = 6.2, 11.7 Hz, 4H), 3.13-3.16 (m, 8H), 3.06 (t, *J* = 8.8 Hz, 4H), 2.99 (t, *J* = 8.4 Hz, 4H), 2.36 (m, 8H), 1.40 (m, 8H), 1.25 (m, 24H), 0.84 (t, *J* = 6.6 Hz, 12H); ^{13}C{H} NMR (125 MHz, DMSO-d_6) δ 153.6, 143.9, 138.5, 125.4, 123.3, 122.0, 102.6, 77.4, 77.1, 73.8, 70.6, 61.8, 61.6, 43.7, 37.5, 31.8, 29.4, 28.1, 22.6, 14.3.

Resorcin[4]arene Cavitand Glycoconjugate 3 (RCG3).[10a] Pale yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 (s, 4H), 5.68 (d, *J* = 6.2 Hz, 4H), 7.55 (s, 4H), 4.51 (s, 8H), 4.56-4.68 (m, 16H), 4.25 (d, *J* = 7.7 Hz, 4H), 4.25 (d, *J* = 7.7 Hz, 4H), 4.25 (m, 12H), 4.10 (m, 4H), 3.93 (m, 4H), 3.68 (d, *J* = 9.9 Hz, 4H), 3.46 (dd, *J* = 5.9, 11.7 Hz, 4H), 3.15-3.19 (m, 8H), 3.08 (t, *J* = 9.2 Hz, 4H), 3.00 (t, *J* = 8.7 Hz, 4H), 2.33 (m, 8H), 1.26 (m, 24H), 1.40 (m, 8H), 0.85 (t, *J* = 6.6 Hz, 12H); ^{13}C{H} NMR (125 MHz, DMSO-d_6) δ 153.7, 144.0, 138.1, 125.4, 124.6, 122.4, 103.4, 99.6, 77.5, 77.1, 73.7, 70.5, 67.9, 63.8, 61.8, 61.6, 50.1, 37.3, 31.9, 29.8, 29.4, 28.2, 22.6, 14.3.

Resorcin[4]arene Cavitand Glycoconjugate 5 (RCG5).[10a] Pale yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.68 (s, 4H), 7.78 (s, 4H), 7.75 (d, *J* = 8.5 Hz, 8H), 7.13 (d, *J* = 8.5 Hz, 8H), 5.86 (d, *J* = 7.3 Hz, 4H), 4.90 (d, *J* = 12.7 Hz, 4H), 4.71 (d, *J* = 12.7 Hz, 8H), 4.51 (d, *J* = 7.3 Hz, 4H), 4.31 (d, *J* = 7.7 Hz, 12H), 3.71 (d, *J* = 11.3 Hz, 4H), 3.43-3.47 (m, 4H), 3.16 (m, 8H), 3.06 (t, *J* = 9.2 Hz, 4H), 3.00 (t, *J* = 8.3 Hz, 4H), 2.50 (m, 8H), 1.45 (m, 8H), 1.22-1.33 (m, 24H), 0.88 (t, *J* = 6.6 Hz, 12H); ^{13}C{H} NMR (125 MHz, DMSO-d_6) δ 158.8, 154.0, 145.3, 138.5, 130.8, 123.0, 122.2, 116.0, 102.7, 99.9, 77.4, 77.1, 73.8, 70.6, 62.0, 61.6, 61.3, 37.3, 31.9, 29.7, 9.3, 28.2, 22.6, 14.3.

General procedure for thiocyanation reaction in water. Alkyl/aryl bromide (1.0 mmol) and KSCN (1.1 equiv./Br) were added into 10 mL of water. **RCG1** (1 mol%) was then added and the reaction mixture was heated to 80 ^{0}C in oil bath. After completion, the reaction mixture was allowed to cool at room temperature, followed by extraction the product with DCM (5 mL x 2) and the combined organic layer was dried over Na_2SO_4. DCM was concentrated and NMR spectra were recorded.

General procedure for thiazole formation in water. α-thiocyanato propiophenone (1.0 mmol) and aniline derivative (1.1 mmol) were added into 10 mL of water. **RCG3** (1 mol%) was then added and the reaction mixture was heated to 80 ^{0}C for 1 hr in oil bath. After completion, the reaction mixture was allowed to cool at room temperature, followed by extraction the product with ethyl acetate (5 mL x 2) and the combined organic layer was dried over Na_2SO_4. Ethyl acetate was concentrated, and NMR spectra were recorded.

General procedure for one-pot thiazole formation in water. α-bromo propiophenone (1.0 mmol) and potassium thiocyanate (1.1 mmol) were added into 10 mL of water. **RCG3** (1 mol%) was then added and the reaction mixture was heated to 80 ^{0}C for 30 min. Aniline derivative (1.1 mmol) was then added to the solution and the reaction mixture was ran for 1 hr at 80 ^{0}C. After completion, the reaction mixture was allowed to cool at room temperature, followed by extraction the product with ethyl acetate (5 mL x 2) and the combined organic layer was then dried over Na_2SO_4. Ethyl acetate was concentrated, and NMR spectra were recorded.

5-methyl-*N*,4-diphenylthiazol-2-amine (1b). Yellow solid in 218 mg (82 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.21-7.32 (m, 5H), 7.01 (t, *J* = 7.1 Hz, 1H), 2.44 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 161.2, 145.9, 140.5, 134.9, 129.3, 128.5, 128.3, 127.4, 122.7, 118.0, 166.5, 12.3.

2-((5-methyl-4-phenylthiazol-2-yl)amino)phenol (2b). Brown solid (276 mg, 98 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 6.85 (t, *J* = 7.3 Hz, 1H), 6.80 (m, 1H), 2.40 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 160.3, 146.2, 144.6, 135.2, 129.4, 128.3, 127.9, 127.0, 122.0, 119.2, 118.7, 116.5, 11.9. HRMS (ESI) m/z: (M + H)$^+$ Calcd for $C_{16}H_{15}N_2OS^+$ 283.0900; Found 283.0907.

3-((5-methyl-4-phenylthiazol-2-yl)amino)phenol (3b). Brown solid (273 mg, 97 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.64 (d, *J* = 7.7 Hz, 2H), 7.42-7.45 (m, 4H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 2H), 2.39 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 160.8, 152.5, 145.7, 135.8, 133.9, 128.7, 128.4, 127.4, 119.5, 115.9, 12.4.

4-((5-methyl-4-phenylthiazol-2-yl)amino)phenol (4b). Brown solid (276 mg, 98 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.64 (d, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.41 (m, 1H), 7.31 (d, *J* = 7.1 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 2.39 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 160.4, 152.1, 145.2, 135.3, 133.5, 128.2, 128.0, 126.9, 119.0, 115.4, 115.1, 12.0.

***N*-(2-methoxyphenyl)-5-methyl-4-phenylthiazol-2-amine (5b).** Yellow solid (287 mg, 97 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 6.6 Hz, 1H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.35 (m, 1H), 6.97 (m, 2H), 6.88 (d, *J* = 7.7 Hz, 1H), 3.88 (s, 3H), 2.49 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 159.5, 147.2, 146.7, 135.2, 130.1, 128.3, 128.2, 127.4, 121.4, 121.0, 115.7, 101.0, 55.6, 12.2.

***N*-(3-methoxyphenyl)-5-methyl-4-phenylthiazol-2-amine (6b).** Yellow solid (284 mg, 96 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.29 (m, 1H), 7.12 (t, *J* = 8.2 Hz, 2H), 6.84 (t, *J* = 2.2 Hz, 1H), 6.69-6.71 (dd, *J* = 1.7, 8.0 Hz, 1H), 6.53-6.55 (dd, *J* = 2.1, 8.2 Hz, 1H), 3.71 (s, 3H), 2.45 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 161.3, 160.4, 145.7, 141.8, 134.9, 129.9, 128.4, 128.2, 127.3, 116.5, 110.4, 108.2, 103.7, 55.1, 12.3.

***N*-(4-methoxyphenyl)-5-methyl-4-phenylthiazol-2-amine (7b).** Brown solid (287 mg, 98 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.26 (m, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 2.38 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 164.2, 156.0, 146.0, 134.1, 128.5, 128.1, 127.2, 122.0, 115.3, 114.4, 55.4, 12.2.

5-methyl-4-phenyl-*N*-(*o*-tolyl)thiazol-2-amine (8b). Yellow solid (274 mg, 98 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 9.10 (s, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.31 (m, 1H), 7.18 (m, 2H), 6.97 (d, *J* = 7.6 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 161.3, 145.1, 139.6, 130.5, 128.6, 128.2, 128.0, 127.0, 126.4, 123.0, 120.7, 116.3, 18.1, 12.0.

5-methyl-4-phenyl-*N*-(*p*-tolyl)thiazol-2-amine (9b). Orange solid (277 mg, 99 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.25 (m, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 2.39 (s, 3H), 2.31 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 162.1, 145.5, 138.1, 134.8, 132.5, 129.8, 128.4, 128.2, 127.3, 118.7, 115.8, 20.7, 12.2.

***N*-(4-fluorophenyl)-5-methyl-4-phenylthiazol-2-amine (14b).** Yellow solid (249 mg, 88 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 7.67-7.72 (m, 2H), 7.66 (t, *J* = 8.6 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 8.8 Hz, 2H), 2.41 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 159.3, 145.2, 137.9, 135.1, 128.3, 127.0, 118.1, 115.5, 115.3, 11.9.

***N*,4-diphenylthiazol-2-amine (17b).** Brown solid (204 mg, 81 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 7.93 (d, *J* = 6.9

Hz, 2H), 7.76 (d, *J* = 7.3 Hz, 2H), 7.43 (m, 2H), 7.36 (m, 2H), 7.30 (s, 3H), 6.97 (m, 1H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 163.1, 150.1, 141.2, 134.5, 130.0, 128.6, 127.5, 125.7, 121.2, 116.8, 102.8.

2-((4-phenylthiazol-2-yl)amino)phenol (18b). Yellow solid (230 mg, 86 %);^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.49 (s, 1H), 8.30 (s, 1H), 7.89 (d, *J* = 5.0 Hz, 2H), 7.25-7.29 (m, 2H), 6.88 (m, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 164.2, 149.5, 146.3, 134.6, 129.3, 128.6, 127.4, 125.6, 122.3, 119.0, 115.1, 103.2.

3-((4-phenylthiazol-2-yl)amino)phenol (19b). Brown solid (228 mg, 85 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 9.45 (s, 1H), 7.94 (d, *J* = 7.3 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.39 (s, 1H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.28 (s, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.08 (m, 1H), 6.44 (d, *J* = 7.2 Hz, 1H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 163.1, 158.0, 150.1 142.3, 134.6, 129.7, 128.6, 127.6, 125.8, 108.6, 107.9, 104.1, 102.8.

4-((4-phenylthiazol-2-yl)amino)phenol (20b). Brown solid (239 mg, 89 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.14 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.18 (s, 1H), 6.78 (d, *J* = 8.7 Hz, 2H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 164.3, 152.3, 150.1, 134.7, 133.6, 128.6, 127.6, 125.6, 119.3, 115.5, 101.8.

4-phenyl-*N*-(*o*-tolyl)thiazol-2-amine (21b). Brown solid (221 mg, 83 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.91 (d, *J* = 7.3 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.27 (s, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 2.26 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 163.3, 150.1, 138.8, 134.6, 130.1, 129.4, 128.6, 127.5, 125.6, 120.5, 117.0, 20.4.

4-phenyl-*N*-(*p*-tolyl)thiazol-2-amine (22b). Brown solid (215 mg, 81 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.25 (s, 2H), 7.22 (s, 1H), 7.01 (t, *J* = 7.2 Hz, 2H), 2.31 (s, 3H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 165.4, 149.9, 139.4, 134.7, 130.6, 128.8, 128.5, 127.4, 126.5, 125.6, 123.3, 120.9, 102.8, 18.1.

***N*-(3-fluorophenyl)-4-phenylthiazol-2-amine (23b).** Yellow solid (197 mg, 73 %); ^{1}H NMR (100 MHz, DMSO-d_6) δ 10.54 (s, 1H), 7.91 (d, *J* = 7.7 Hz, 2H), 7.83 (d, *J* = 12.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.30-7.39 (m, 4H), 6.78 (t, *J* = 7.5 Hz, 1H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 162.7, 150.2, 147.8, 134.4, 130.6, 128.7, 127.7, 125.6, 112.7, 107.5, 107.3, 103.6.

***N*-(4-fluorophenyl)-4-phenylthiazol-2-amine (24b).** Green solid (189 mg, 70 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.77-7.80 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 8.4 Hz, 2H), 7.20 (t, *J* = 8.9 Hz, 2H); ^{13}C{H} NMR (100 MHz, DMSO-d_6) δ 163.2, 150.0, 137.8, 134.5, 128.6 127.6, 125.7, 118.4, 115.6, 115.4, 102.8.

ASSOCIATED CONTENT

Supporting Information

NMR spectral data for **RCG1**, **RCG3**, **RCG5** and 2-amino-1,3-thiazole compounds **1b-9b**, **14b**, **17b-24b** and HRMS (ESI) spectral data for the unknown thiazole **2b**, are included.

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Notes

The authors declare no competing financial interest

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