ACS Sustainable Chemistry & Engineering

Research Article

Cite This: ACS Sustainable Chem. Eng. 2018, 6, 5852−5857

pubs.acs.org/journal/ascecg

Pure Water-Induced Dehalogenation of 2,4-Di-*tert*-amino-6-substituted-5-halogenopyrimidines

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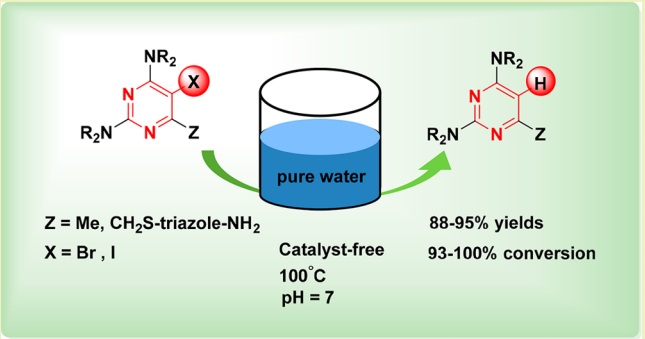
Supporting Information

ABSTRACT: Dehalogenation of 5-halogenopyrimidine derivatives in boiling pure water was accomplished in high yields. The substrate and pure water are the only two reaction components in this process. Dehalogenation takes place in the absence of any catalysts, additives, basic, or acidic conditions, introducing water as a potential dehalogenation reagent.



KEYWORDS: *5-Halopyrimidine, Dehalogenation, Water, Green, Catalyst-free, Deuterodebromination*

INTRODUCTION

While most synthetic methods have been developed to be productive in anhydrous organic media, recent progress in the field of water-mediated organic reactions has triggered more interest in organic chemistry. Poor solubility of reactants and multiple side-effect observations have limited the use of water in organic synthesis. However, low cost, safety, natural availability, and green identity of water have prompted chemists to testify organic reactions in water which already have been working well in organic solvents.[1,2]

Among the recently reported water-based organic reactions, carbon−halogen bond reduction is of the most challenging and important transformations.[1] Poor solubility of organohalides in water has limited application of water as solvent in such processes. Most recent methodologies involve C−X bond reduction of aryl halides using palladium[3,4] and zinc[5,6] in water/aqueous media; some other methods relies on UV excitation[7] and irradiation in the presence of a sensitizer,[8] and some are only applicable to water-soluble organohalides.[9,10] These reports besides similar unexpected observations[11] show that potential of water either as a medium or a reagent could be taken into more consideration for this type of reduction. In this regard we investigated dehalogenation of 5-halogenopyrimidines in water. Except for a few examples,[8] a literature survey disclosed that halogenated pyrimidines have been mainly reduced in organic media in the presence of transition metal catalysts like palladium[12−15] or zinc dust,[16] as well as by hot hydroiodic acid,[17] *p*-toluenesolphonyl hydrazine,[18] and electrolysis at Mercury cathodes.[19]

Herein, we report a green, high yielding straightforward dehalogenation of 5-halogenopyrimidine derivatives in neutral pure water both as reagent and medium for the first time.

RESULTS AND DISCUSSION

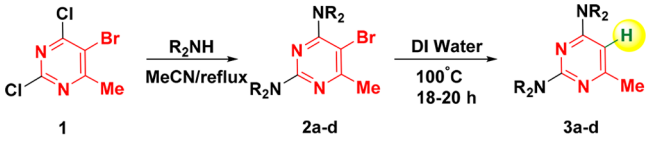
The idea that H_2O can participate in dehalogenation of 5-halogenopyrimidine derivatives, first came to us when 6-methyl-2,4-dimorpholinopyrimidine (**3d**) was partially obtained from 5-bromo-6-methyl-2,4-dimorpholinopyrimidine (**2d**) during a synthetic process in ethanol (Scheme 1). It was further found that compound **2d** could be converted to **3d** with 40% yield after 24 h in boiling ethanol as the sole reactant and solvent. A literature survey disclosed that dehalogenation of similar substrates in aqueous alcoholic solvents proceeds only through irradiation.[8,20−22] Meanwhile our further investigations revealed that no product was obtained in boiling absolute ethanol under inert atmosphere. This observation prompted us to consider probable incorporation of water in this process. Surprisingly further experiments proved water, in charge of C−X bond reduction in 5-halogenated pyrimidines. In fact, compound **2d** could be fully converted into 3d in boiling deionized (DI) water under neutral condition in the absence of any other reactants or additives. Accordingly, we prepared a number of similar substrates for further reduction in boiling water. For this purpose, two synthetic pathways were designed for preparation of 5-bromo-2,4-diamino-6-substituted pyrimidines from their precursors as described in Schemes 1 and 2.

As shown in Scheme 1, compounds **2a−d** were synthesized on subjecting 5-bromo-2,4-dichloro-6-methylpyrimidine (**1**) to the mixture of secondary amines in acetonitrile. Further treatment of the newly synthesized 5-bromopyrimidines in DI

Received: November 8, 2017
Revised: March 5, 2018
Published: March 20, 2018

DOI: 10.1021/acssuschemeng.7b04127
ACS Sustainable Chem. Eng. 2018, 6, 5852−5857

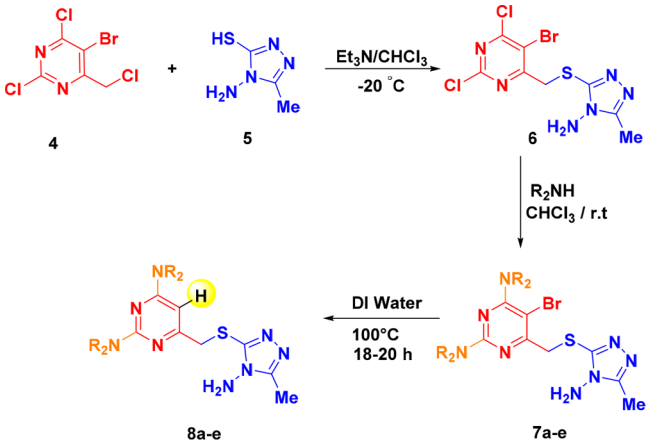
Scheme 1. Synthetic Route to the Formation of Compuonds 2 and 3[a]



entry	— NR_2	product	Conv%	yield%
1	*a*	3a	98	92
2	*b*	3b	100	93
3	*c*	3c	93	88
4	*d*	3d	100	95

[a]All the reactions were performed under normal condition (air and normal light).

Scheme 2. Synthetic Pathway Leading to the Formation of 8[a]



entry	— NR_2	product	Conv%	yield%
1	*a*	8a	94	90
2	*b*	8b	95	90
3	*c*	8c	100	94
4	*d*	8d	98	92
5	*e*	8e	95	91

[a]All the reactions were performed under normal condition (air and normal light).

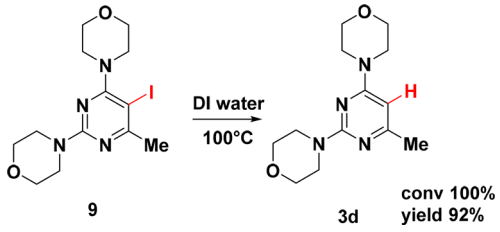
water, delivered the debrominated products **3a–d** in high conversion rates and yields.

As illustrated in Scheme 2, 5-bromo-2,4-dichloro-6-(chloromethyl)pyrimidine (**4**) which was synthesized by an established method,[23] was reacted with 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol (**5**) at −20 °C to give the substituted product **6**. Reaction of **6** with various secondary amines afforded compounds **7a–e**. Compounds **8a–e** were successfully obtained on submission of **7a–e** to boiling DI water in high yields and conversion rates, as well.

As could be seen in Schemes 1 and 2, all the substrates were debrominated under the similar conditions in pure water at 100 °C. It is noteworthy that the observed conversions and yields are not much affected by different substituents at positions 2,4 and 6 of pyrimidine. The reactions were clean and the products could be obtained from water directly after concentration.

To expand the scope of this process on reducing other halogeno pyrimidines, compound **3d** as the model substrate was iodinated to 5-iodo-6-methyl-2,4-dimorpholino pyrimidine (**9**) and further subjected to boiling DI water. As expected, the dehalogenated product was obtained in high conversion and yield (Scheme 3).

Scheme 3. Example of the Substrate Deiodination



To study how different reaction conditions can influence the rate of the process, we attempted the conversion of **2d** to **3d**, as the model reaction in different media. In $HCl_{(aq)}$ medium, a mixture of both the starting material and product was obtained. In concentrated $HCl_{(aq)}$ (5 or 12 M) a mixture containing the product and several byproducts were obtained; 6-chloromethyl-2,4-dimorpholinopyrimidine was the only byproduct, which could be identified (Table 1, entries 1–4). These results show that aqueous acidic media are not as suitable as pure water for this process. Under the same reaction conditions, no product was detected on submitting **2d** to $KOH_{(aq)}$ (Table 1, entry 5). The rate of conversion decreased to 48% and 25% in the mixture of 1:1 and 1:3 H_2O: EtOH, respectively (Table 1, entries 6 and 7). This result indicates that when the combination of water with alcohol is demanding, the smaller portions of alcohol can provide the better conversion rates since it would neither decrease the reaction temperature remarkably nor compete with H_2O to attack the halopyrimidine. It is noteworthy that the conversion rate in water at temperatures below 85 °C was negligible and reduction did not take place at room temperature even within the days. As could be concluded from these observations, performing the reaction in boiling neutral deionized water afforded the best result. However, deviation from pure water medium to other aqueous media consisting of other compounds like reductants, soft bases, solvents miscible with water, etc., can affect the reaction results (Table 1). For example, the use of Zn, Fe, $K_2S_2O_5$ powders as reductants (entries 9–11) or NaSCN and NaI as soft bases (entries 13 and 14) can accelerate the process, while the use of ethylene glycol and glycerol retards and decreases the yield of the reaction respectively (entries 16 and 17). Entries 8,

DOI: 10.1021/acssuschemeng.7b04127
ACS Sustainable Chem. Eng. 2018, 6, 5852−5857

Table 1. Dehalogenation of Compound 2d to 3d in Water in Different Media[a]

entry	medium	time (h)	conv (%)	yield (%)/mgr[b]
1[c]	HCl (0.2 M)	18	30	10/4
2[c]	HCl (1 M)	18	33	13/4
3[c]	HCl (5 M)	18	72	18/8
4[c]	HCl (12 M)	18	100	23/10
5[d]	KOH (5 or 12 M)	18	-	-
6[e]	EtOH:H_2O (3:1)	18	34	25/11
7[e]	EtOH:H_2O (1:1)	18	52	48/20
8[f]	H_2O	18	100	95/42
9[g]	Zn	2	95	86/38
10[g]	Fe	2	88	72/32
11[g]	$K_2S_2O_5$	1.5	100	81/36
12[g]	H_2O	2	43	38/16
13[g]	NaSCN	5.5	100	84/38
14[g]	NaI	5.5	98	89/40
15[g]	H_2O	5.5	60	52/22
16[h]	ethylene glycol	10	55	41/18
17[h]	glycerol	10	100	73/32
18[i]	H_2O	10	86	79/36
19[j]	AIBN/DMF	18	100	88/39

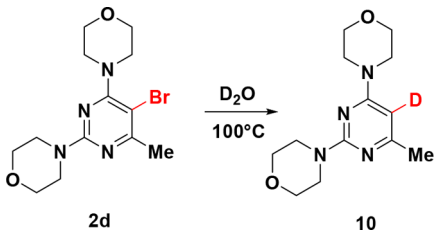
[a]Quantities and conditions: compound **2d** = 0.2 mmol (60 mgr, 1equiv), T = 100 °C. [b]Measured and isolated by TLC on silica gel polygram STL G/UV 254 plates using *n*-hexane:ethyl acetate (2:1) as eluent. [c]$HCl_{(aq)}$ = 10 mL. [d]$KOH_{(aq)}$ = 10 mL; trace amounts of the reaction conversions and product yields were observed in 1 and 0.2 M $KOH_{(aq)}$. [e]EtOH:H_2O = 20 mL, T = 78−80 °C, ambient pressure. [f]Water = 10 mL. [g]Water = 12 mL, solid additives = 6 equiv. [h]Cosolvent:H_2O (1:1) = 8 mL, T = 115−118 °C. [i]Water = 4 mL. [j]H_2O:DMF (5:1) = 12 mL, AIBN = 5 equiv.

12, 15, and 18 show the reaction progress in pure water the absence of their related additives or cosolvents.

To explore the mechanism of this reaction, we conducted a set of experiments:

When the reaction was performed in D_2O at 100 °C, the product was completely deuterated at position 5, showing that water is in charge of hydrogen transfer to the substrate. Scheme 4, exemplifies deuterodebromination of **2d** as the representative substrate to deuterated derivative **10**.

Scheme 4. Example for Deuterodebromination of the Model Substrate

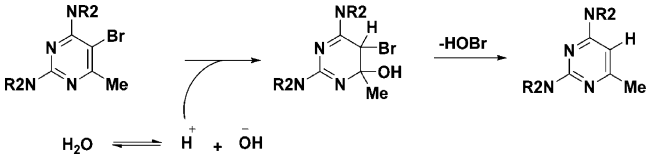


2d 10

In addition, the probable role of light and O_2 was excluded in this process since the reaction could also proceed successfully in dark and under argon atmosphere, as same as under normal condition (air and normal light). Moreover, no inhibition was observed on performing the reaction in the presence of AIBN (azobis(isobutyronitrile)) as a source of radical in boiling water−DMF mixture; showing that the reaction is not proceeding through a radical pathway (Table 1, entry 19).

Based on these observations, it seems likely that dehalogenation of 5-halogenopyrimidines in pure water proceeds via an electrophilic aromatic substitution mechanism (Scheme 5).

Scheme 5. Possible Route for Dehalogenation of 5-Halogenopyrimidines in Pure Water



According to the proposed mechanism, hydrogen is added to the substrate by an initial attack of the nucleophilic C-5 atom of pyrimidine on proton. The reaction follows through elimination of HOBr from the intermediate to afford the reduced product.

A notable increase in acidity of medium at the end of the reaction shows that bromide is existing as acid species like HOBr in the residual solution, probably in equilibrium with HBr. Performing the reaction in different concentrations of the starting material showed that the decrease in pH values was proportional to the increase of the starting material concentration.

Although there were not enough evidence to support the presence of OBr^- in the solution and the results of ion chromatography analysis proved the presence of Br^-, loss of an HOBr molecule is necessary for the intermediate to rearomatize to the product and thus, is mechanistically supported. The labile HOBr can further undergo several competitive decomposition and disproportionation reactions to reproduce HBr in the solution.[24,25]

CONCLUSION

A number of 2,4-diamino-6-substituted-5-halogenopyrimidines were dehalogenated on submission to DI water at 100 °C within 18−20 h with excellent conversion and yields. As a literature survey revealed, this research presents the first report on dehalogenation of organohalides in pure water as both medium and dehalogenation reagent. The reaction is so green, straightforward, and proceeds under neutral conditions without using irradiation or other chemicals. Derivatives carrying NH_2 and sulfide functionalities could tolerate the reaction conditions. This observation may provide another option to the synthetic chemist for hydrodehalogenation of 5-halogenopyrimidines during a synthetic procedure. To expand the scope of this process to other organohalides, further studies are underway.

EXPERIMENTAL SECTION

Melting points were measured by an Electrothermal type 9200 melting point apparatus. The ^1H NMR (300 MHz) and the ^{13}C NMR (75 MHz) spectra were obtained on a Bruker Advance DRX-300 Fourier transformer spectrometer using tetramethylsilane as an internal standard. An Avatar 370 FT-IR Thermo Nicolet spectrometer was employed to record the IR spectra and a Varian Mat CH-7 instrument for scanning mass spectra at 70 eV. Micro analytical data were obtained on a Thermo Finnigan Flash EA 1112 microanalyzer.

General Procedure for the Preparation of 2a−d [See Scheme 1]. A mixture of 5-bromo-2,4-dichloro-6-methylpyrimidine **1** (1 mmol, 241 mg) and secondary amine (**a**−**d**) (4 mmol) in acetonitrile was refluxed for 3 h. After removal of the solvent under

DOI: 10.1021/acssuschemeng.7b04127
ACS Sustainable Chem. Eng. 2018, 6, 5852−5857

reduced pressure, the residue was washed with water and recrystallized from ethanol to afford the desired products.

General Procedure for Preparation of Compounds 7a−e [See Scheme 2]. 4-Amino-5-methyl-4*H*-1,2,4-triazole-3-thiol **5** (1 mmol, 130 mg) was added with vigorous stirring to a solution of compound **4** (1 mmol, 274 mg) and Et_3N (1.5 mmol, 0.2 mL) in chloroform (3 mL) at −20 °C. The reaction was monitored by TLC ($CHCl_3$: MeOH, 20:1) and after completion, secondary amine (**a−e**) (4 mmol) was added at room temperature. The completion of reaction occurred within hours. The solvent was evaporated under reduced pressure. The crude product was washed with water and recrystallized from ethanol to give **7a−e**.

General Procedure for Preparation of 3a−d and 8a−e. A mixture of 5-bromo-6-substituted-2,4-diaminopyrimidine, **2a−d** or **7a−e**, (0.5 mmol) and pure water (20 mL) was refluxed with stirring for 18−20 h. After the completion of reaction, the solution was neutralized with KOH_{aq} (1 M) and concentrated under reduced pressure. The solid residue was filtered off and washed with water to give the desired dehalogenated product.

*5-Bromo-4-methyl-2,6-di(pyrrolidin-1-yl)pyrimidine (**2a**).* White powder, yield = 0.28 g, 92%; mp = 57−59 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 3.78−3.72 (4H, m), 3.66- 3.49 (4H, m), 2.43 (3H, s), 1.99- 1.87 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C); δ 165.1, 159.2, 157.9, 90.5, 49.9, 46.5, 26.0, 25.7, 25.6. FTIR (KBr disk, ν_{max}): 2964 (s), 2867 (s), 1540 (s). MS (*m*/*z*) 310 (M^+). Anal. Calcd for $C_{13}H_{19}BrN_4$: C, 50.17; H, 6.15; N, 18.00. Found: C, 50.10; H, 6.18; N, 18.07.

*5-Bromo-4-methyl-2,6-di(piperidin-1-yl)pyrimidine (**2b**).* White powder, yield = 0.32 g, 95%; mp = 37−39 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 3.75−3.71 (4H, m), 3.43−3.39 (4H, m), 2.43 (3H, s), 1.71−1.57 (12 H, m). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 165.9, 164.1, 159.2, 95.41, 49.7, 44.8, 25.8, 25.7, 24.9, 24.7. FTIR (KBr disk, ν_{max}): 2933 (s), 2849 (s), 1547 (s). MS (*m*/*z*) 338 (M^+). Anal. Calcd for $C_{15}H_{23}BrN_4$: C, 53.10; H, 6.83; N, 16.51. Found: C, 53.17; H, 6.72; N, 16.60.

*5-Bromo-4-methyl-2,6-bis(4-methylpiperidin-1-yl)pyrimidine (**2c**).* White powder, yield = 0.34 g, 95%; mp = 85−87 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 4.72−4.66 (2H, m), 4.10−4.02 (2H, m), 2.78 (t, 4H, *J* = 15), 2.43 (s, 3H), 1.73−1.66 (m, 5H), 1.42−1.09 (m, 5H), 0.99 (two overlapping doublets, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 165.9, 164.0, 159.2, 95.4, 94.0, 44.3, 34.0, 31.3, 31.1, 25.7, 22.08, 22.04. FTIR (KBr disk, ν_{max}): 2994 (m), 2915 (s), 2836 (s),1544 (s). MS (*m*/*z*) 366 (M^+). Anal. Calcd for $C_{17}H_{27}BrN_4$: C, 55.59; H, 7.41; N, 15.25. Found: C, 55.59; H, 7.47; N, 15.29.

*4,4′-(5-Bromo-6-methylpyrimidine-2,4-diyl)dimorpholine (**2d**).* White powder, yield = 0.33 g, 98%; mp = 71−73 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 3.73 (t, 4H, *J* = 4.5), 3.66 (s, 8H), 3.40 (t, 4H, *J* = 4.8), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 166.7, 163.6, 159.1, 96.3, 66.8, 66.7, 48.9, 44.3, 25.5. MS (*m*/*z*) 342 (M^+). Anal. Calcd for $C_{13}H_{19}BrN_4O_2$: C, 45.49; H, 5.58; N, 16.32. Found: C, 45.46; H, 5.55; N, 16.22.

*4-Methyl-2,6-di(pyrrolidin-1-yl)pyrimidine (**3a**).* White powder; yield = 0.10 g, 92%; mp = 70−73 °C (77−78 °C literature).[26] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.54 (s, 1H), 3.82−3.78 (m, 4H), 3.67−3.64 (m, 4H), 2.26 (s, 3H), 2.01−1.92 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C); δ 165.0, 159.9, 159.1, 91.5, 47.2, 46.2, 25.9, 25.6, 24.9. MS (*m*/*z*) 231 (M^+). Anal. Calcd for $C_{13}H_{20}N_4$: C, 67.21; H, 8.68; N, 24.12. Found: C, 67.36; H, 8.73; N, 24.21.

*4-Methyl-2,6-di(piperidin-1-yl)pyrimidine (**3b**).* Yellowish powder, yield = 0.11 g, 93%; mp = 107−110 °C (118 °C literature).[27] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.69 (s, 1H), 3.73−3.71 (m, 4H), 3.53−3.50 (m, 4H), 2.21 (s, 3H), 1.62−1.55 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 165.8, 163.0, 161.9, 90.9, 44.9, 44.8, 25.9, 25.5, 25.1, 24.8, 24.6. MS (*m*/*z*) 260 (M^+). Anal. Calcd for $C_{15}H_{24}N_4$: C, 69.19; H, 9.29; N, 21.52. Found: C, 69.13; H, 9.22; N, 21.55.

*4-Methyl-2,6-bis(4-methylpiperidin-1-yl)pyrimidine (**3c**).* Colorless viscous oil (separated from the neutralized concentrated solution by decantation); yield = 0.12 g, 88%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.64 (s, 1H), 4.63 (d, 2H, *J* = 12), 4.23 (d, 2H, *J* = 12), 2.67 (t, 4H, *J* = 15), 2.13 (s, 3H), 1.60−1.44 (m, 5H), 1.17−1.00 (m, 5H), 0.86 (d, 6H, *J* = 6). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 165.7, 162.9, 161.8, 91.0, 44.3, 44.2, 34.2, 33.8, 31.4, 31.3, 24.5, 22.1, 21.9. FTIR (KBr disk, ν_{max}): 2949 (s), 2920 (s), 2846 (s), 1652 (m),1577 (s). MS (*m*/*z*) 287 (M^+ − 1). Anal. Calcd for $C_{17}H_{28}N_4$: C, 70.79; H, 9.79; N, 19.42. Found: C, 70.81; H, 9.77; N, 19.45.

*4,4′-(6-Methylpyrimidine-2,4-diyl)dimorpholine (**3d**).* Off-white powder, yield = 0.12 g, 95%; mp = 113−116 °C (126−128 °C literature).[28] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.78 (s, 1H), 3.79−3.76 (m, 12H), 3.56 (t, 4H, *J* = 5.1), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 166.5, 163.4, 161.7, 91.8, 67.0, 66.6, 44.3, 44.2, 24.5. MS (*m*/*z*) 264 (M^+). Anal. Calcd for $C_{13}H_{20}N_4O_2$: C, 59.07; H, 7.63; N, 21.20. Found: C, 59.09; H, 7.61; N, 21.15.

*3-(((5-Bromo-2,6-di(piperidin-1-yl)pyrimidin-4-yl)methyl)thio)-5-methyl-4H-1,2,4-triazol-4-amine (**7a**).* White powder, yield = 0.25 g, 55%; mp = 85−88 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 4.76 (s, 2H, D_2O exchangeable), 4.27 (s, 2H), 3.62−3.68 (m, 4H), 3.44−3.45 (m, 4H), 2.46 (s, 3H), 1.57−1.66 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 166.1, 164.0, 163.5, 158.9, 153.9, 93.2, 49.6, 45.0, 41.1, 29.6, 25.7, 24.6, 24.5, 10.5. FTIR (KBr disk, ν_{max}): 3354 (m), 3199 (m), 2931 (s), 2850 (s), 1646 (w), 1546 (s) cm^{-1}. MS (*m*/*z*) 387 (M^+ − 79). Anal. Calcd for $C_{18}H_{27}BrN_8S$: C, 46.25; H, 5.82; N, 23.97; S, 6.86. Found: C, 46.23; H, 5.85; N, 23.91; S, 6.79.

*3-(((5-Bromo-2,6-bis(4-methylpiperidin-1-yl)pyrimidin-4-yl)-methyl)thio)-5-methyl-4H-1,2,4-triazol-4-amine (**7b**).* Off-white powder, yield = 0.28 g, 58%; mp = 69−71 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 4.68 (s, 2H, D_2O exchangeable), 4.43 (d, 2H, *J* = 12.9), 4.18 (s, 2H), 4.02 (d, 2H, *J* = 12.6), 2.70 (q, 4H, *J* = 12.9), 2.37 (s, 3H), 1.63−1.47 (m, 6H), 1.29−1.21 (m, 2H), 1.09−1.0 (m, 2H), 0.91 (two overlapping doublets, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 164.1, 163.4, 158.9, 153.8, 150.5, 93.3, 48.9, 44.2, 41.5, 33.9, 31.1, 31.0, 21.96, 21.93, 10.59. FTIR (KBr disk, ν_{max}): 3227 (s), 3122 (m), 2995 (w), 2913 (s), 1611 (w), 1542 (s) cm^{-1}. MS (*m*/*z*) 415 (M^+ − 79). Anal. Calcd for $C_{20}H_{31}BrN_8S$: C, 48.48; H, 6.31; N, 22.62; S, 5.86. Found: C, 48.48; H, 6.36; N, 22.64; S, 6.46.

*3-(((5-Bromo-2,6-dimorpholinopyrimidin-4-yl)methyl)thio)-5-methyl-4H-1,2,4-triazol-4-amine (**7c**).* Off-white powder, yield = 0.30 g, 65%; mp = 142−144 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 4.68 (s, 2H, D_2O exchangeable), 4.38 (s, 2H), 3.82 (t, 4H, *J* = 4.2 Hz), 3.753 (t, 4H, *J* = 3.9 Hz), 3.68 (t, 4H, *J* = 3.9), 3.54 (t, 4H, *J* = 4.2), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 163.7, 163.6, 158.8, 153.7, 150.5, 94.3, 66.6, 66.5, 48.8, 44.2, 40.5, 10.4. FTIR (KBr disk, ν_{max}): 3329 (m), 3272 (w), 3143 (m), 2953 (m), 2916 (m), 2854 (m), 1644 (w), 1547 (s) cm^{-1}. MS (*m*/*z*) 391 (M^+ − 79). Anal. Calcd for $C_{16}H_{23}BrN_8O_2S$: C, 40.77; H, 4.92; N, 23.77; S, 6.80. Found: C, 40.67; H, 4.82; N, 23.89; S, 6.74.

*3-(((5-Bromo-2,6-bis(4-phenylpiperazin-1-yl)pyrimidin-4-yl)-methyl)thio)-5-methyl-4H-1,2,4-triazol-4-amine (**7d**).* Off-white powder, yield = 0.37 g, 60%; mp = 92−94 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.21 (t, 5H, *J* = 7.8), 6.90−6.80 (m, 5H), 4.68 (s, 2H, D_2O exchangeable), 4.29 (s, 2H), 3.79−3.75 (m, 4H), 3.62−3.59 (m, 4H), 3.23−3.21 (m, 4H), 3.14−3.12 (m, 4H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 163.7, 163.6, 158.8, 153.7,151.2, 151.1, 150.5, 129.26, 129.24, 120.3, 120.1, 116.5, 116.2, 94.2, 49.3, 48.9, 48.3, 43.8, 40.9, 10.5. FTIR (KBr disk, ν_{max}): 3322 (m), 3155 (m), 3057 (w), 2913 (m), 2845 (m), 1599 (s), 1544(s) cm^{-1}. MS (*m*/*z*) 540 (M^+ − 79). Anal. Calcd for $C_{28}H_{33}BrN_{10}S$: C, 54.10; H, 5.35; N, 22.53; S, 5.13. Found: C, 54.10; H, 5.32; N, 22.55; S, 5.13.

*6-(((4-Amino-5-methyl-4H-1,2,4-triazol-3-yl)thio)methyl)-5-bromo-N2,N2,N4,N4-tetraethylpyrimidine-2,4-diamine (**7e**).* White powder, yield = 0.22 g, 50%; mp = 83−85 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.26 (s, 2H, D_2O exchangeable), 4.35 (s, 2H), 3.63 (q, 4H, *J* = 6.9), 3.66−3.47 (m, 4H), 2.46 (s, 3H), 1.25 (t, 6H, *J* = 6.9), 1.17−1.10 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 164.5, 161.0, 157.1, 154.2, 149.7, 100.8, 44.7, 43.3, 41.3, 13.2, 10.5. FTIR (KBr disk, ν_{max}): 3319 (m), 3166 (m), 2974 (m), 2931 (m), 2872 (w), 1555 (s). MS (*m*/*z*) 362 (M^+ − 79). Anal. Calcd for $C_{16}H_{27}BrN_8S$: C,

DOI: 10.1021/acssuschemeng.7b04127
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43.34; H, 6.14; N, 25.27; S, 7.23. Found: C, 43.45; H, 6.13; N, 25.29; S, 7.26.

*3-(((2,6-Di(piperidin-1-yl)pyrimidin-4-yl)methyl)thio)-5-methyl-4H-1,2,4-triazol-4-amine (**8a**).* Yellowish powder, yield = 0.17 g, 90%; mp = 70−72 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.71 (s, 1H), 4.95 (s, 2H, D_2O exchangeable), 3.88 (s, 2H), 3.69−3.66 (m, 4H), 3.55−3.53 (m, 4H), 2.44 (s, 3H), 1.66−1.58 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 164.0, 162.8, 162.0, 153.9, 150.3, 90.89, 45.0, 44.7, 41.7, 29.7, 25.8, 25.5, 24.9, 24.7, 10.5. FTIR (KBr disk, ν_{max}): 3402 (m), 3235 (m), 2935 (m), 2851 (m), 1654 (s), 1617 (s). MS (m/z) 388 (M^+). Anal. Calcd for $C_{18}H_{28}N_8S$: C, 55.64; H, 7.26; N, 28.84; S, 8.25. Found: C, 55.60; H, 7.19; N, 28.78; S, 8.20.

*3-(((2,6-Bis(4-methylpiperidin-1-yl)pyrimidin-4-yl)methyl)thio)-5-methyl-4H-1,2,4-triazol-4-amine (**8b**).* Yellowish powder, yield = 0.18 g, 90%; mp = 65−67 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 6.08 (s, 1H), 5.40 (s, 2H, D_2O exchangeable), 4.43 (d, 2H, J = 13.2), 4.22 (s, 2H), 3.72−3.55 (m, 2H), 2.85−2.78 (m, 4H), 2.40 (s, 3H), 1.71−1.55 (m, 5H), 1.18−1.04 (m, 5H), 0.90 (two overlapping doublets, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 161.4, 160.9, 154.8, 149.0, 93.6, 27.2, 61.7, 52.31, 51.0, 45.6, 33.8, 33.7, 30.9, 30.8, 29.7, 21.6, 21.5, 10.6. FTIR (KBr disk, ν_{max}): 3272 (m), 3149 (m), 2948 (s), 2921(s), 2849 (s), 1613(m), 1577 (s). MS (m/z) 416 (M^+). Anal. Calcd for $C_{20}H_{32}N_8S$: C, 57.66; H, 7.74; N, 26.90; S, 7.70. Found: C, 57.58; H, 7.69; N, 26.94; S, 7.60.

*3-(((2,6-Dimorpholinopyrimidin-4-yl)methyl)thio)-5-methyl-4H-1,2,4-triazol-4-amine (**8c**).* Yellowish powder, yield = 0.17 g, 94%; mp = 168−170 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.84 (s, 1H), 4.77 (s, 2H, D_2O exchangeable), 4.01 (s, 2H), 3.77−3.71 (m, 12H), 3.55 (t, 4H, J = 6), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 164.4, 163.2, 161.7, 153.7, 150.3, 91.7, 66.9, 66.5, 44.3, 44.2, 40.5, 10.51. FTIR (KBr disk, ν_{max}): 3321 (m), 3077 (m), 2962 (m), 2854 (m), 1577 (s). MS (m/z) 392 (M^+). Anal. Calcd for $C_{16}H_{24}N_8O_2S$: C, 48.96; H, 6.16; N, 28.55; S, 8.17. Found: C, 48.85; H, 6.12; N, 28.28; S, 8.10.

*3-(((2,6-Bis(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methyl)thio)-5-methyl-4H-1,2,4-triazol-4-amine (**8d**).* Off-white powder, yield = 0.24 g, 92%; mp = 63−65 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.41−7.32 (m, 4H), 7.01−6.81 (m, 6H), 5.89 (s, 1H), 4.81 (s, 2H, D_2O exchangeable), 4.02 (s, 2H), 3.93−3.90 (m, 4H), 3.80−3.77 (m, 4H), 3.25−3.20 (m, 8H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 164.5, 163.0, 161.7, 153.8, 151.4, 151.0, 150.3, 129.28, 129.23, 120.3, 120.2, 116.5, 116.4, 91.7, 49.4, 49.2, 49.1, 43.8, 40.8, 10.5. FTIR (KBr disk, ν_{max}): 3278 (br, m), 2921 (m), 2851 (m), 1653 (s) 1616 (s). MS (m/z) 413 (M^+ − 129). Anal. Calcd for $C_{28}H_{34}N_{10}S$: C, 61.97; H, 6.31; N, 25.81; S, 5.91. Found: C, 61.80; H, 6.11; N, 25.73; S, 5.82.

*6-(((4-Amino-5-methyl-4H-1,2,4-triazol-3-yl)thio)methyl)-N2,N2,N4,N4-tetraethylpyrimidine-2,4-diamine (**8e**).* Viscous oil; yield = 0.16 g, 91%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.85 (s, 1H), 5.07 (s, 2H, D_2O exchangeable), 4.08 (s, 2H), 3.61−3.42 (m, 8H), 2.37 (s, 3H), 1.29−1.16 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 161.2, 159.8, 157.0, 154.2, 150.6, 93.3, 42.7, 42.2, 37.2, 13.0, 12.9, 10.5. FTIR (KBr disk, ν_{max}): 3268 (m), 3143 (m), 2975 (s), 2933 (s), 1654 (s), 1612 (s). MS (m/z) 363 (M^+ − 1). Anal. Calcd for $C_{16}H_{28}N_8S$: C, 52.72; H, 7.74; N, 30.74; S, 8.80. Found: C, 52.88; H, 7.61; N, 30.82; S, 8.78.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.7b04127.

^{1}H NMR, ^{13}C NMR, FTIR, and mass spectra (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Research Council of Ferdowsi University of Mashhad is acknowledged for partial support of this work (3/33579). The authors also like to express their gratitude to Dr. Mohamad-Hossein Ahmadzadeh for his useful comments.

■ ABBREVIATIONS

DI water, deionized water; TLC, thin layer chromatography; AIBN, azobis(isobutyronitrile)

■ REFERENCES

(1) Li, C. J. Organic reactions in aqueous media-with a focus on carbon-carbon bond formation. *Chem. Rev.* **1993**, *93* (6), 2023.

(2) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley & Sons: New York, 1997.

(3) Suzuka, T.; Sueyoshi, H.; Maehara, S.; Ogasawara, H. Reactivity of Aryl Halides for Reductive Dehalogenation in (Sea) water Using Polymer-Supported Terpyridine Palladium Catalyst. *Molecules* **2015**, *20* (6), 9906.

(4) Bhattacharjya, A.; Klumphu, P.; Lipshutz, B. H. Ligand-Free, Palladium-Catalyzed Dihydrogen Generation from TMDS: Dehalogenation of Aryl Halides on Water. *Org. Lett.* **2015**, *17* (5), 1122.

(5) Isley, N. A.; Hageman, M. S.; Lipshutz, B. H. Dehalogenation of functionalized alkyl halides in water at room temperature. *Green Chem.* **2015**, *17* (2), 893.

(6) Hekmatshoar, R.; Sajadi, S.; Heravi, M. M. Reductive dehalogenation of arylhalides and alkylhalides with zinc in THF saturated aqueous ammonium chloride. *J. Chin. Chem. Soc.* **2008**, *55* (3), 616.

(7) Kwok, W. M.; Zhao, C.; Li, Y. L.; Guan, X.; Wang, D.; Phillips, D. L. Water-catalyzed dehalogenation reactions of isobromoform and its reaction products. *J. Am. Chem. Soc.* **2004**, *126* (10), 3119.

(8) Venkatarangan, L.; Yang, D. H.; Epling, G. A.; Basu, A. K. Debromination of 8-bromo-2′-deoxyguanosine by methylene blue and visible light. *Tetrahedron Lett.* **1999**, *40* (8), 1441.

(9) Jang, D. O. Hypophosphorous acid mediated dehalogenation in water. *Tetrahedron Lett.* **1996**, *37* (30), 5367.

(10) Light, J.; Breslow, R. A water soluble tin hydride reagent. *Tetrahedron Lett.* **1990**, *31* (21), 2957.

(11) Seela, F.; Zulauf, M.; Becher, G. Unexpected dehalogenation of 3-bromopyrazolo [3, 4-d] pyrimidine nucleosides during nucleobase-anion glycosylation. *Nucleosides Nucleotides* **1997**, *16* (3), 305.

(12) Campbell, J. B.; Whitehead, C. W.; Kress, T. J.; Moore, L. L. The selective dehalogenation of 2, 4-dichloro-5-[2, 4-dichlorodiphenyl-methyl] pyrimidine. *Ann. N. Y. Acad. Sci.* **1973**, *214* (1), 216.

(13) Tikad, A.; Dehbi, O.; Akssira, M.; Aadil, M.; Massip, S.; Leger, J. M.; Jarry, C.; Guillaumet, G.; Routier, S. Efficient access to 2, 7-diarylated pyrido [3, 2-d] pyrimidines involving regioselective palladodehalogenation and Suzuki cross-coupling reactions. *Synthesis* **2013**, *45* (04), 491.

(14) Whittaker, N.; Jones, T. S. G. A new synthesis and the chemical properties of 5-aminopyrimidine. *J. Chem. Soc.* **1951**, 1565.

(15) Smith, V. H.; Christensen, B. E. Pyrimidines. v. dehalogenation and nuclear reduction of certain pyrimidines1. *J. Org. Chem.* **1955**, *20* (7), 829.

DOI: 10.1021/acssuschemeng.7b04127
ACS Sustainable Chem. Eng. 2018, 6, 5852−5857

(16) Boarland, M. P. V.; McOmie, J. F. W. Monosubstituted pyrimidines, and the action of thiourea on chloropyrimidines. *J. Chem. Soc.* **1951**, *272*, 1218.
(17) Brown, D. J.; Waring, P. Pyrimidine reactions. The dehalogenation of 2-halogenopyrimidines by hydriodic acid. *Aust. J. Chem.* **1973**, *26* (2), 443.
(18) Berecz, G.; Reiter, J.; Csaszar, J. Non catalytic dehalogenation of some 5-chloro-1, 2, 4-triazolo [1, 5-a] pyrimidine derivatives. *J. Heterocycl. Chem.* **1999**, *36* (5), 1199.
(19) Ji, C.; Peters, D. G.; Davidson, E. R. Electrochemical reduction of halogenated pyrimidines at mercury cathodes in acetonitrile. *J. Electroanal. Chem.* **2001**, *500* (1), 3.
(20) Matasović, B.; Bonifačić, M. Reductive dehalogenation of 5-bromouracil by aliphatic organic radicals in aqueous solutions; electron transfer and proton-coupled electron transfer mechanisms. *Radiat. Phys. Chem.* **2011**, *80* (6), 750.
(21) Swanson, B. J.; Kutzer, J. C.; Koch, T. H. Photoreduction of 5-bromouracil. Ionic and free-radical pathways. *J. Am. Chem. Soc.* **1981**, *103* (5), 1274.
(22) Dietz, T. M.; Koch, T. H. Photochemical reduction of 5-bromouracil by cysteine derivatives and coupling of 5-bromouracil to cystine derivatives. *Photochem. Photobiol.* **1989**, *49* (2), 121.
(23) Bazazan, T.; Bakavoli, M.; Rahimizadeh, M.; Eshghi, H.; Nikpour, M. Synthesis of a novel fused tricyclic heterocycle, pyrimido [5, 4-e][1, 4] thiazepine, and its derivatives. *Heterocycl. Commun.* **2013**, *19* (6), 401−404.
(24) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, 2nd ed.; Butterworth-Heinemann: UK, 1997.
(25) Rich, R. *Inorganic Reactions in Water*, 1st ed.; Springer Science and Business Media: USA, 2007.
(26) Papanikos, A.; Eklund, J.; Jackson, W. R.; Kenche, V. B.; Campi, E. M.; Robertson, A. D.; Jarrott, B.; Beart, P. M.; Munro, F. E.; Callaway, J. K. Cyclic voltammetry as an indicator of antioxidant activity. *Aust. J. Chem.* **2002**, *55* (5), 205−212.
(27) Brown, D. M.; Kon, G. A. Some heterocyclic analogues of stilbenes. *J. Chem. Soc.* **1948**, 2147.
(28) Garner, J.; Hill, T.; Odell, L.; Keller, P.; Morgan, J.; McCluskey, A. Identification of aminopyrimidine regioisomers via line broadening effects in ^{1}H and ^{13}C NMR spectroscopy. *Aust. J. Chem.* **2004**, *57* (11), 1079.

DOI: 10.1021/acssuschemeng.7b04127
ACS Sustainable Chem. Eng. 2018, 6, 5852−5857