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COMMUNICATION

Structure-dependent tautomerization induced catalyst-free autocatalyzed N-alkylation of heteroaryl amines with alcohols†

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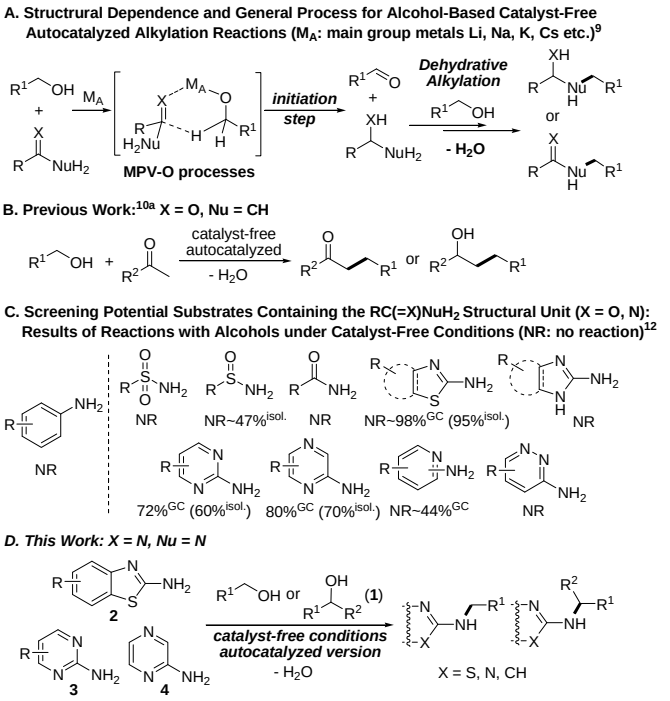
Catalyst-free autocatalyzed dehydrative N-alkylation reactions of 2-aminobenzothiazoles, 2-aminopyrimidines, and 2-aminopyrazine with primary and secondary alcohols have been achieved for efficient, practical, and green synthesis of the versatile heteroaryl amine derivatives. These reactions were interestingly induced by structure-dependent tautomeric equilibriums of the heteroaryl amines via MPV-O transfer hydrogenation of the imino tautomers by alcohols to give aldehydes as the key initiating step.

Developing efficient, practical, and green methods[1] for C-N bond formation is a major topic in synthetic chemistry, because the organonitrogen compounds like amine and amide derivatives are key structures in pharmaceuticals, bioactive molecules, and natural products.[2-4] Due to the green features of readily available alcohols and their advantages as synthetic reagents, transition metal (TM)-catalyzed anaerobic dehydrogenative *N*-alkylation reactions of amines and amides with alcohols, namely the borrowing hydrogen or hydrogen autotransfer methodology,[4,5] have recently become a useful way to achieve the versatile amine and amide derivatives. To develop greener and more practical alcohol-based alkylation methods, we have previously reported air-promoted TM-catalyzed aerobic N- and C-alkylation reactions[6] and related aerobic imination reactions of alcohols and amines.[7] During our continuous studies and based on an extensive survey of the literature, we gradually realized that, in addition to the known anaerobic dehydrogenation strategy,[4,5] there should be more greener, more practical, but still efficient protocols for alcohol activation.[8] Later, we accidentally found that lone aldehyde could also catalyze the N- and C-alkylation reactions of amides, amines, and secondary alcohols with primary alcohols.[9] More interestingly, we also observed that substrate ketones could even act as the catalyst in C-alkylation of methyl ketones with alcohols, which led to catalyst-free autocatalyzed C-alkylation methods for selective synthesis of the ketone or alcohol products (Scheme 1A-1B).[10a]



Scheme 1. Alcohol-based catalyst-free autocatalyzed alkylation reactions: general process, structural dependence, and substrate design/discovery.

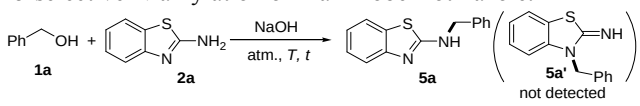
Further analysis of this catalyst-free autocatalyzed alkylation reaction suggested that it is most likely a $RC(=X)NuH_2$ structural unit-dependent process (Scheme 1A), which involves a crucial initial aldehyde generation step accomplished by transfer hydrogenation of $RC(=X)NuH_2$ by alcohols *via* the key

TM-free Meerwein-Pondorf-Verley-Oppenauer (MPV-O) process.[9-11] Since we have also observed that C=N double bonds of imine intermediates could also be reduced by alcohols *via* MPV-O process,[9a] we hypothesized that certain amines or amides bearing the typical $RC(=X)NH_2$ structural unit (X = O or N, Nu = N) should also meet the requirements for the catalyst-free reactions and thus can undergo the alkylation reactions without any external catalysts[12] (Scheme 1C). However, such reactions have not been described in the literature yet.[4-6,9] Herein we report an advance in the field by describing structure-dependent tautomerization-induced catalyst-free autocatalyzed dehydrative N-alkylation reactions of 2-aminobenzothiazoles (**2**), 2-aminopyrimidines (**3**), and 2-aminopyrazine (**4**) with primary and secondary alcohols (**1**), which provides an efficient, practical, and green method for synthesis of the useful heteroaryl amine derivatives without using any external catalysts such as TM catalysts[4-6] or aldehydes[9] (Scheme 1D).

To test the supposed theory of structural dependence, anilines without $RC(=X)NH_2$ structure were firstly investigated under catalyst-free conditions (Scheme 1C).[13] To avoid aldehyde contamination in the alcohols and the presence of air in the reactions that can lead to misguiding results,[6,9] redistilled pure alcohols **1** (100% purity) were used and the reactions were strictly degassed and then heated under nitrogen. In agreement with the hypothesis, no reaction occurred or only trace product was detected in the reactions of anilines. Then, various sulfonamides, sulfinamides, carboxylic amides, and heteroaryl amines bearing the typical $RC(=X)NH_2$ structural unit were investigated to figure out which can undergo the catalyst-free autocatalyzed alkylation reactions.[13] For some substrates, no target reaction occurred at all, or only low yields of the target products were detected. To our delight, 2-aminobenzothiazole (**2a**), 2-aminopyrimidine (**3a**), and 2-aminopyrazine (**4**) behaved differently under the catalyst-free conditions and their reactions efficiently afforded good to high yields of the target products in the presence of a suitable base.[12] These results revealed that substrates that can conform to the requirements of catalyst-free autocatalyzed alkylation process indeed exist in a broad scope.

The reaction conditions of 2-aminobenzothiazole **2a** were firstly optimized. As shown in Table 1, the neat mixture of pure benzyl alcohol **1a** and **2a** was initially heated at 120 °C under nitrogen with 20 mol% NaOH,[9a,12] giving a high isolated yield of a new product in only 6 h (entry 1). Spectra analysis of the product showed that, different to the known N-alkylation of 2-aminobenzothiazoles **2** with alkyl halides that occurred at the more basic *endo*-nitrogen and gave *endo*-N-alkylated **5a'**,[3] the present reaction gave specifically the *exo*-N-alkylated **5a** as the sole product. The reaction was so fast (entry 1) that it was still very efficient at a lower temperature of 100 °C (entries 2-3). Then, running the reaction under air or directly using the commercial **1a** can both shorten the reaction time (entries 4-5). Therefore, the best result was obtained by running the reaction at 100 °C under air directly using commercial **1a**, giving **5a** in 93% isolated yield (entry 6). Base screening and further attempts to reduce the loading of NaOH and the reaction temperature gave no better result.[13]

Table 1. Condition optimization for catalyst-free autocatalyzed *exo*-selective N-alkylation of 2-aminobenzothiazole.[a]



entry	additive (mol%)	atm., *T*, *t*	**5a**%[b]
1[c]	-	N_2, 120 °C, 6 h	98 (95)
2[c]	-	N_2, 100 °C, 6 h	82 (78)
3[c]	-	N_2, 100 °C, 12 h	96 (84)
4[c]	-	air, 100 °C, 6 h	98 (92)
5[d]	-	N_2, 100 °C, 6 h	97 (90)
6[d]	-	***air, 100 °C, 6 h***	***99 (93)***
7[c]	$Ph_2C=CH_2$ (20 mol%)	N_2, 100 °C, 6 h	(80)
8[c]	TEMPO (20 mol%)	N_2, 100 °C, 6 h	(93)
9[c]	in dark	N_2, 100 °C, 6 h	(73)

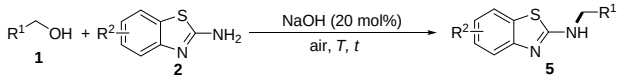
[a] The mixture of **1a** (1.5 mmol, 1.5 equiv.), **2a** (1 mmol), and NaOH (20 mol%)[9] sealed in a 10 mL Schlenk tube was heated and monitored by GC-MS and/or TLC. [b] GC yields (isolated yields in parenthesis) based on **2a**. [c] **1a** of 100% purity was used. [d] Commercial **1a** (>99% purity) was directly used.

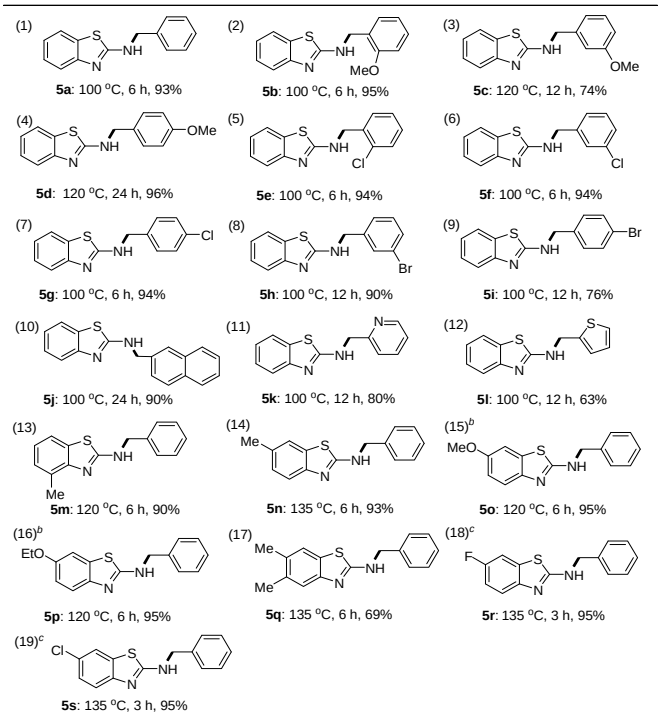
To prove or exclude the reaction's possibility of undergoing the radical mechanism in the presence of bases, control reactions **1a** and **2a** with radical scavengers or in dark were examined. As shown in Table 1, the reaction of pure **1a** and **2a** with 1,1-diphenylethylene as radical scavenger gave a close yield of **3a** (entry 7) with that of the blank reaction (entry 2). Another reaction with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) gave a higher yield of **3a** under the same conditions (entry 8). This is mostly because TEMPO is not only a radical scavenger, but also a co-catalyst in aerobic alcohol oxidation reactions[7] that can initiate the N-alkylation of amines by direct conversion of alcohols to aldehydes.[9a] Moreover, the reaction in dark also gave a good yield of **3a** (entry 9). All these results clearly revealed that these control reactions preceded equally well under the radical-free conditions (entries 7-9) with the blank reaction (entry 2). Therefore, the possibility of a radical participated process in present catalyst-free N-alkylation reaction can be excluded.

The above optimized condition (Table 1, entry 6) was then applied to other alcohols and 2-aminobenzothiazoles to extend the scope of the *exo*-selective dehydraitve N-alkylation reaction. As shown in Table 2, for the reactions of unsubstituted **2a**, it reacted with various benzylic (entries 1-10) and heterobenzylic alcohols (entries 11-12), including those bearing the more bulky substituents (entries 2, 5, 10) and those with more reactive halide groups (entries 5-9), to give good to high yields of the *exo*-N-alkylation products under similar conditions. For some substituted alcohols, they required longer reaction times (12-24 h) or a higher temperature of 120 °C. This is similar with the reactions of substituted 2-aminobenzothiazoles and **1a** (entries 13-19), which generally required higher temperatures of 120-135 °C. This is most possibly due to the higher melting points of the substituted substrates and the adopted solvent-free condition of the present method, because, for some substrates, once the reactions reached a higher temperature, they could

become very fast (entries 13-19, 3-6 h). As shown in the table, substrates bearing the reactive halide groups were tolerated under basic conditions to give the target amines (entries 5-9, 18-19), which are useful building blocks in synthetic chemistry. As to reactions using aliphatic alcohols as the alkylating reagents, although we tried many times, they were found not reactive in present reactions even under harsher conditions like higher temperatures and more amounts of bases, giving only trace yields of the products.

Table 2. Catalyst-free autocatalyzed *exo*-N-alkylation of 2-aminobenzothiazoles with alcohols.[a]

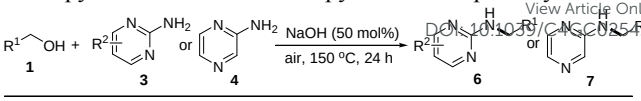


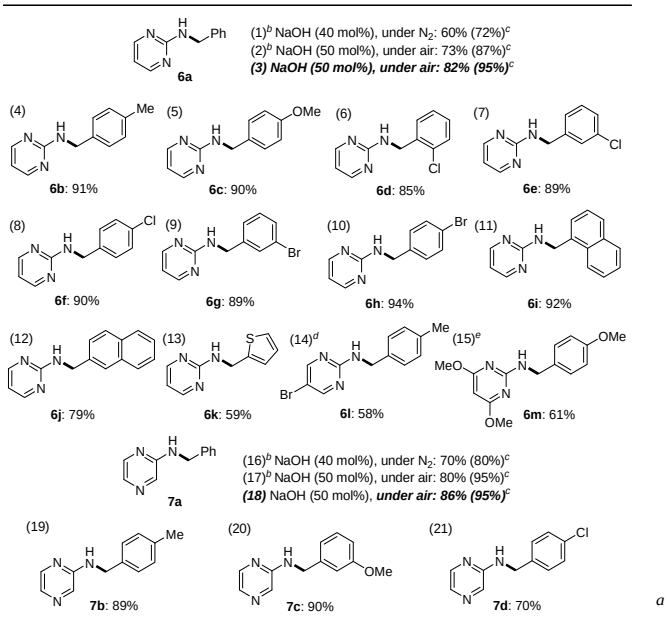


[a] Unless otherwise noted, see entry 6 of Table 1 for similar conditions. Isolated yields based on 2. [b] 2 equiv. **1a**. [c] 3 equiv. **1a**.

We then investigated the catalyst-free reactions of alcohols with 2-aminopyrimidines (**3**) and 2-aminopyrazine (**4**). As shown in Table 3, the initial reaction of pure **1a** with **3a** and **4** under N_2 at 150 °C readily gave 60% and 70% isolated yields of the target product **6a** and **7a**, respectively (entries 1 and 16), suggesting amines **3a** and **4** also belong to the family of catalyst-free autocatalyzed alkylation reactions. Then, running the reactions with more amounts of NaOH under air gave higher product yields (entries 2 and 17). Similar to the reaction of **2a** (Table 1, entry 5), the reactions of **3a** and **4** under air using directly commercial **1a** gave even better results, affording the highest yields of both **6a** and **7a** (Scheme 3, entries 3 and 18). The reactions were also investigated using various bases or at lower temperatures, but they gave only lower yields of the products.[13]

Table 3. Catalyst-free autocatalyzed N-alkylation of 2-aminopyrimidines and 2-aminopyrazine with primary alcohols.[a]





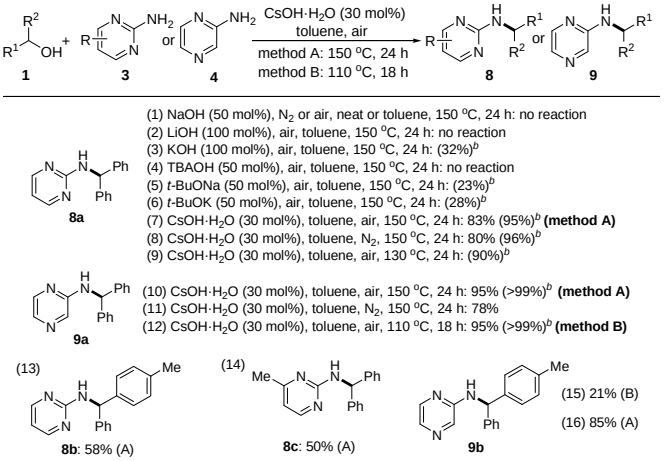
[a] See Table 1 for similar conditions.[13] Unless otherwise indicated, commercial **1** (>99% purity) was directly used under air. Isolated yields based on **3** or **4**. [b] **1a** of 100% purity was used. [c] Yields in parenthesis are GC yields. [d] 80 mol% NaOH. [e] 80 mol% LiOH.

The optimized conditions were then applied to other alcohols and substituted heteroaryl amines to extend the scope of the method. Thus, **3a** and **4** readily reacted with substituted benzylic alcohols (entries 4-12, 19-21) and a heterobenzylic alcohol (entry 13), including the *ortho*-substituted and more bulky ones (entries 6, 11, 12) and those bearing the reactive halide groups (entries 6-10, 21), to give good to high yields of the target products under the standard conditions. For electron-deficient 2-aminopyrimidine bearing a 5-Br moiety, the reaction was less efficient and required more amounts of NaOH to ensure an effective reaction (entry 14). In the case of 4,6-dimethoxyl-2-aminopyrimidine, the product was obtained in only a low yield due to formation of transetherification byproducts in the presence of NaOH. Base screening showed that LiOH is the best one, giving 61% isolated yield of the target **6m** (entry 15).

The more challenging catalyst-free N-alkylation reaction with secondary alcohols was also attempted. Secondary alcohols have not been successfully used in the catalyst-free C-alkylation reactions.[10a] In fact, they were also seldom used in alcohol-based dehydrative alkylation reactions.[4-6,8-10] As shown in Table 4, the reaction of 2-aminopyrimidine **3a** and benzohydrol was initially performed under the preceding optimized conditions using NaOH as the base. However, no reaction occurred either under neat or solvent conditions, either under air or under nitrogen (entry 1). Then, other alkali bases

like LiOH, KOH, CsOH, *t*-BuONa, *t*-BuOK, and even TBAOH (tetrabutylammonium hydroxide) were carefully screened under neat or solvent conditions (entries 2-7).[13] The results showed that CsOH is a much better base, giving a high yield of the target product **8a** with only 30 mol% of CsOH in toluene (entry 7, method A). The same reaction under nitrogen also gave a similar high yield of **8a** (entry 8), suggesting this is also a catalyst-free reaction. Further optimization of the reaction condition at lower temperatures gave a lower yield of **8a** (entry 9).

Table 4. Catalyst-free autocatalyzed N-alkylation of 2-aminopyrimidines and 2-aminopyrazine with secondary alcohols.[a]



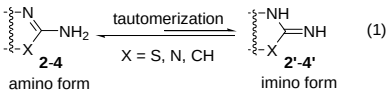
(1) NaOH (50 mol%), N_2 or air, neat or toluene, 150 °C, 24 h: no reaction
(2) LiOH (100 mol%), air, toluene, 150 °C, 24 h: no reaction
(3) KOH (100 mol%), air, toluene, 150 °C, 24 h: (32%)[b]
(4) TBAOH (50 mol%), air, toluene, 150 °C, 24 h: no reaction
(5) *t*-BuONa (50 mol%), air, toluene, 150 °C, 24 h: (23%)[b]
(6) *t*-BuOK (50 mol%), air, toluene, 150 °C, 24 h: (28%)[b]
(7) CsOH·H_2O (30 mol%), toluene, air, 150 °C, 24 h: 83% (95%)[b] **(method A)**
(8) CsOH·H_2O (30 mol%), toluene, N_2, 150 °C, 24 h: 80% (96%)[b]
(9) CsOH·H_2O (30 mol%), toluene, air, 130 °C, 24 h: (90%)[b]
(10) CsOH·H_2O (30 mol%), toluene, air, 150 °C, 24 h: 95% (>99%)[b] **(method A)**
(11) CsOH·H_2O (30 mol%), toluene, N_2, 150 °C, 24 h: 78%
(12) CsOH·H_2O (30 mol%), toluene, air, 110 °C, 18 h: 95% (>99%)[b] **(method B)**

[a] See Table 1 for similar conditions.[12] Isolated yields based on **3** or **4**. [b] Yields in parenthesis are GC yields.

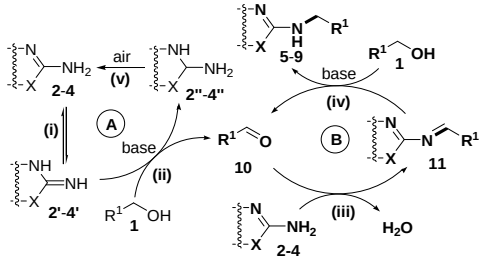
The same condition was then applied to 2-aminopyrazine **4**. As shown in Table 4, the reactions of **4** and benzohydrol under air and under nitrogen both gave good to high yields of the target product **9a** (entries 10-11), indicating that this is also a catalyst-free reaction. Temperature screening showed that the reaction is still efficient at 110 °C, giving a high yield of **9a** in 18 h (entry 12, method B). The optimized conditions A and B were then applied to substituted substrates. With 2-aminopyrimidines **3**, the reactions were less efficient and gave moderate yields of products **8b-c** (entries 13-14). With 2-aminopyrazine **4**, the reaction with a substituted benzohydrol was not efficient at 110 °C (entry 15). Thus, the reaction was heated at 150 °C to give a good yield of product **9b** (entry 16).

The above results that different amines and amides bearing the similar RC(=X)NH_2 structural unit behaved great differently from non-reactive to lowly reactive to even highly reactive under catalyst-free conditions aroused our attention in the mechanism of these interesting N-alkylation reactions. We originally speculated that alcohols should able to reduce the C=X bond of RC(=X)NH_2 unit in the presence of a suitable main group base to give the initiating aldehydes (Scheme 1A). However, this is clearly not the fact because no reaction occurred with some potential substrates like carboxylic amides (Scheme 1C), which is close to methyl ketones in structure.[10a]

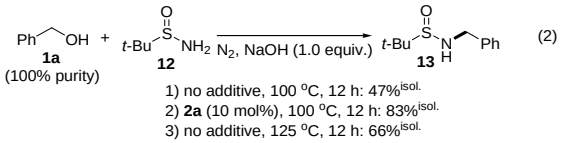
Besides, the preceding observations neither support the base-mediated radical mechanism in these reactions (Table 1). We later noticed that tautomeric equilibriums always exist with many heterocycle compounds,[3,14] i.e., the heteroaryl amines should exist in both amino and imino tautomers (eq. 1). We realized that this may be the key to the success of heteroaryl amines **2-4** and may also be responsible for the observed moderate reactivities of aminopyridines and sulfinamides (Scheme 1C). Therefore, a possible mechanism supported by additional experimental findings (*vide infra*) was proposed for these catalyst-free autocatalyzed N-alkylation reactions (Scheme 2).



As shown in Scheme 2, due to the presence of the more reactive terminal C=N double bond, the imino tautomers of heteroaryl amines **2-4**, **2'-4'**, may react efficiently with alcohols **1** in the presence of a base to give catalytic amounts of the key initiating aldehydes **10** and the reduced heterocylic amines **2''-4''** via TM-free MPV-O processes (step ii). It is hard to detect the existence of aldehyde **10** in the reaction mixtures, but its catalytic activity to promote an originally ineffective reaction can be observed to prove the formation of aldehdyes in the reaction mixtures. As shown in eq. 2, the blank reaction of the less reactive sulfinamide **12** and **1a** afforded only 47% yield of target **13** (entry 1 or Scheme 1C). In contrast, addition of only 10 mol% of 2-aminobenzothiazole (**2a**) greatly promoted the reaction to finally give 83% **13** under the same conditions (entry 2), suggesting that **10** should be generated from the reaction of 10 mol% **2a** and **1a** (Scheme 2, step ii) and then greatly promoted the reaction of **12** and **1a**, just as in the catalyst-free autocatalyzed reactions of **2-4** with the alcohols. Indeed, when the blank reaction of **1a** and **12** was heated at 125 °C to achieve a more efficient autocatalyzed aldehyde generation process at higher temperatures, **13** could be obtained in a higher yield of 66% (entry 3). These results further supported step ii in the proposed mechanism that the rate of aldehyde generation is dependent on the structure of the amine substrate and also the reaction temperature, which led to varied reactivities of the amine substrates under catalyst-free conditions (Scheme 1C) and higher reactivities at higher temperatures.

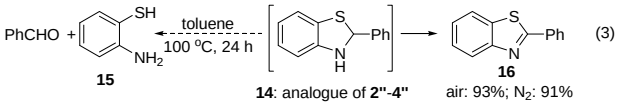


Scheme 2. Possible mechanism for catalyst-free autocatalyzed N-alkylation of heteroaryl amines with alcohols induced by structure-dependent tautomerization.



Consequently, upon generation, aldehyde **10** should quickly condense with **2-4** to give imine intermediates **11** (step iii), which was further transfer hydrogenated by alcohols **1** via TM-free MPV-O process[9-11] to give alkylated products **5-9** and regenerate **10** (step iv) to finish the aldehyde-catalyzed dehydrative N-alkylation cycle (cycle B).[9a]

As to cycle A, the reduced heterocylic amines **2''-4''** could not be detected due to their instable nature. We suppose they were oxidized by air to regenerate **2-4** (step v) during the workup. Because, we found heterocycle **14**, an analogue of **2''-4''**, could be easily oxidized to give aromatized **16** when it was prepared *in situ* from **10a** and 2-aminothiophenol **15** either under air or under nitrogen (eq. 3, by *in situ* oxidation in the reaction under air, or by oxidation during workup in the reaction under nitrogen). Therefore, once generated, **2''-4''** may be oxidized by air to regenerate **2-4** in reactions under air (step v), which will further undergo alkylation to give products. This well explains the higher yields of the products obtained from reactions under air than under nitrogen, further supporting cycle A in the proposed mechanism.



In conclusion, we have developed catalyst-free autocatalyzed N-alkylation reactions of 2-aminobenzothiazoles, 2-aminopyrimidines, and 2-aminopyrazine with primary and secondary alcohols, providing an efficient, practical, and green method for synthesis of the versatile heteroaryl amine derivatives without using any external catalysts. Mechanistic studies revealed that these interesting catalyst-free N-alkylation reactions were induced by structure-dependent tautomeric equilibriums of the heteroaryl amines through MPV-O transfer hydrogenation of the imino tautomers by alcohols to give the key initiating aldehydes, which then catalyzed the reactions to complete to the give products. Further application and extension of the catalyst-free alkylation reactions and deeper mechanistic insights are underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: detailed condition screening tables, experimental details, and ^{1}H and ^{13}C NMR spectra of the products. See DOI: 10.1039/c000000x/

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