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One-Pot Aminomethylation of Heteroarenes by Rongalite as *In Situ* C1 Source

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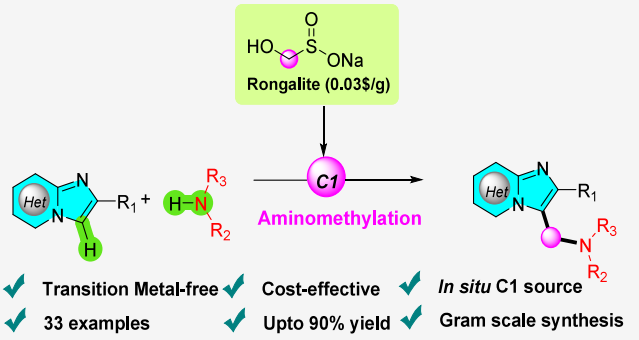
ABSTRACT: Rongalite-mediated one-pot aminomethylation of heteroarenes using secondary amines/anilines has been developed. This transition-metal-free and mild reaction offers an efficient way to synthesize aminomethylated heteroaromatic compounds with high yields and broad functional group tolerance. Here, Rongalite plays a key role in generating the C1 unit source *in situ*, which triggers the aminomethylation process. This approach provides a library of aminomethylated imidazo[1,2-*a*]pyridines and imidazo[2,1-*b*]-thiazoles.



Rongalite, also known as sodium hydroxymethanesulfinate ($NaHOCH_2SO_2$), is a multifunctional reagent that has gained prominence due to its wide applications in organic synthesis.[1] It has unique structural features and serves as the source of (i) sulfoxylate dianion (SO_2^{2-}),[2] (ii) hydride-free reducing agent,[3] (iii) single electron donor[4] and (iv) C1 unit source.[5] The C1 unit source gained much attention from chemists all over the world in recent years, offering novel pathways for constructing complex organic molecules.[6] This allows the introduction of both carbon (C−C) and nitrogen (C−N) bonds in a single step, making it a highly versatile reaction in organic synthesis.

The development of efficient methods for functionalizing heterocyclic compounds is a cornerstone of modern organic chemistry, particularly in the pharmaceutical industry.[7] Imidazoheterocycles are ubiquitous in nature and are key structures in pharmaceuticals[8] (Figure 1) and functional materials.[9]

There has been a recent surge in interest among organic chemists to synthesize and alter the core structure of imidazo[1,2-*a*]pyridines at different positions to increase the biological activities.[10]

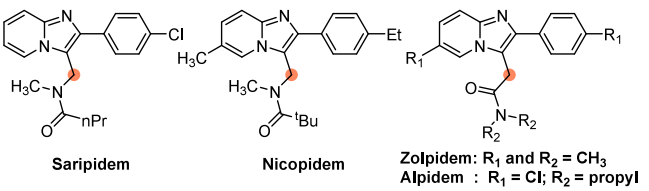


Figure 1. 2-Arylimidazo[1,2-*a*]pyridine containing pharmaceuticals.

The aminomethylation of imidazo[1,2-*a*]pyridine and imidazo[2,1-*b*]thiazole can further enhance these properties by introducing functional groups that improve solubility, receptor binding, and metabolic stability.[11] On the other hand, morpholines are particularly valuable due to their broad range of pharmacological applications, which include acting as antihypertensive, antidepressant and anti-inflammatory agents.[12] By creating hybrids of these pharmacophores through aminomethylation, the biological activities of both morpholines and imidazo[1,2-*a*]pyridine/imidazo[2,1-*b*]thiazoles can be enhanced, leading to the development of new therapeutic agents with improved efficacy and a broader spectrum of action.[13,14] This approach not only expands the chemical space for drug discovery but also provides opportunities for fine-tuning the pharmacokinetic and pharmacodynamic properties of potential drugs.[15] Thus development of methodologies to make this hybrid molecule emerges in organic synthesis. Generally, these hybrid molecules are achieved *via* a) aminomethylation by decarboxylation in the presence of transition-metals (Scheme 1a),[16] b) aminomethylation by oxidative cross-coupling of sp^3- and sp^2-hybridized C−H bonds (Scheme 1b),[17] and c) use of *in situ* C-1 unit source (Scheme 1c).[18]

Although these new methods provide good C1 unit sources, they require harsh reaction conditions, such as the use of

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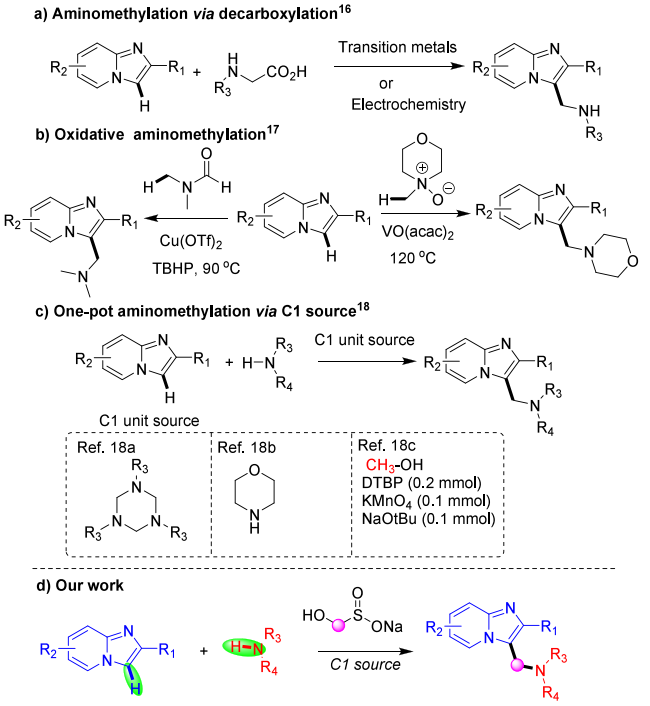
Scheme 1. Strategies for C−C Bond Construction



metals, toxic formalin,[19] long reaction time, risk of over oxidation, use of methanol, expensive reagents, and limited availability.[20] As a result, finding an alternative C1 unit source has become a key goal in one-pot aminomethylation strategies.

Therefore, we aim to develop a novel method for the *in situ* generation of a C1 source to overcome the constraints associated with these methods. In this context, we are utilizing rongalite, a commercially inexpensive reagent (ca. $0.03/g), as a C1 unit source under mild conditions for aminomethylation (Scheme 1d).

To validate our hypothesis, a test reaction was conducted between imidazo[1, 2-*a*]pyridine **1a**, morpholine **2a** and rongalite **3** in CH_2Cl_2 solvent, and the results are outlined in Table 1.

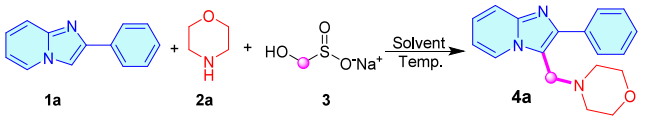
Initially, the reaction mixture was stirred at room temperature for 12 h; no change in the starting material was observed (Table 1, entry 1). Then, the reaction mixture was heated to 45 °C, and surprisingly, the formation of desired product **4a** was observed in a low yield (Table 1, entry 2).

The above result provoked us to optimize the reaction protocol to improve the product yield by changing the reaction conditions, and the results are presented in Table 1. Hence, we have focused on the screening of solvents. The reaction was conducted in other solvents, such as chloroform, dichloroethane and toluene, but gave a low yield (Table 1, entries 3−5).

Later, we changed the reaction medium to other polar aprotic solvents, such as CH_3CN, THF, 1,4-dioxane, DMF, and DMSO, which gave improved yields (Table 1, entries 6−10).

Finally, we have tested the same reaction in polar protic solvents, i.e., methanol and ethanol, which surprisingly gave good yields (Table 1, entries 11 and 12). Ethanol was found to be the best reaction medium among all the solvents tested to produce quantitative yield. To improve the product yield further, we shifted our focus to the stoichiometry of rongalite.

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3 4a

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	CH_2Cl_2	rt	12	n.d[c]
2	CH_2Cl_2	45	12	10
3	$CHCl_3$	65	12	20
4	DCE	70	12	30
5	Toluene	80	10	45
6	CH_3CN	80	12	40
7	THF	70	12	20
8	1,4-Dioxane	70	12	20
9	DMF	90	10	50
10	DMSO	100	12	60
11	MeOH	70	6	70
12	EtOH	70	6	75
13	EtOH	70	5	90[d]
14	EtOH	70	5	90[e]
15	EtOH	70	5	90[f]
16	H_2O	100	24	n.d[c]

[a]All the reactions were conducted in 1.0 mmol scale of **1a** (1.0 mmol), **2a** (1.0 mmol) and **3** (1.0 mmol) in solvent (2 mL), unless otherwise mentioned. [b]Isolated yields. [c]Not detected. [d]1.5 mmol of rongalite used. [e]2.0 mmol of rongalite used. [f]1.5 mmol of morpholine used.

Notably, changing the stoichiometry of rongalite from 1.0 to 1.5 mmol gave the product a 90% yield (Table 1, entry 13). Further increments of rongalite and morpholine did not affect the yield (Table 1, entries 14 and 15). We wanted to test our protocol in water as a reaction medium, but it failed to produce the desired product **4a**, possibly due to solubility issues (Table 1, entry 16).

Later, we tested the substrate scope of the imidazo[1,2-*a*]pyridine with electron-releasing groups such as methyl, methoxy, phenyl, and halogens (−F, −Cl, −Br) on C-2-phenyl, which gave target compounds in good to excellent yields (Scheme 2, **4b−4f**). Substrates that have substitution on the pyridine ring also provided title products in excellent yields (Scheme 2, **4g−4j**). Also, the substitution on both the pyridine ring and C-2-phenyl participated in this reaction and furnished the product in good yields (Scheme 2, **4k−4o**). The electron-withdrawing nitro group on the C-2 phenyl of imidazo[1,2-*a*]pyridine gave a poor yield (Scheme 2, **4p**). Later, we tested our protocol with other secondary amines, such as piperidine, *N*,*N*-diethylamine, and 1,2,3,4-tetrahydroquinoline, which gave satisfactory results (Scheme 2, **4q−4s**). It is worth mentioning that primary amines such as *n*-butylamine and *n*-hexylamine are unreactive under optimized conditions. However, anilines smoothly reacted with rongalite and imidazo[1,2-*a*]pyridine to furnish the target compounds in good yields (Scheme 2, **4t−4w**).

Further, the same reactions conditions were applied to other heteroarenes, i.e., imidazo[2,1-*b*]thiazole and benzo[*d*]-imidazo[2,1-*b*]thiazole, and the results are shown in Scheme 3. A similar reactivity pattern was observed with imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]thiazole, which gave the end products in good yields (Scheme 3, **6a−6j**).

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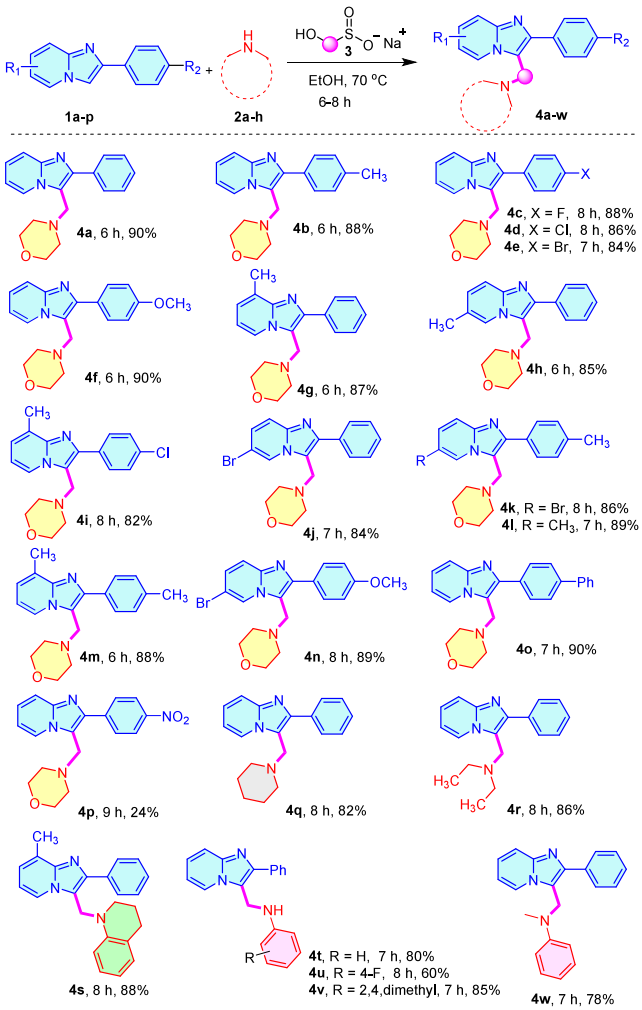
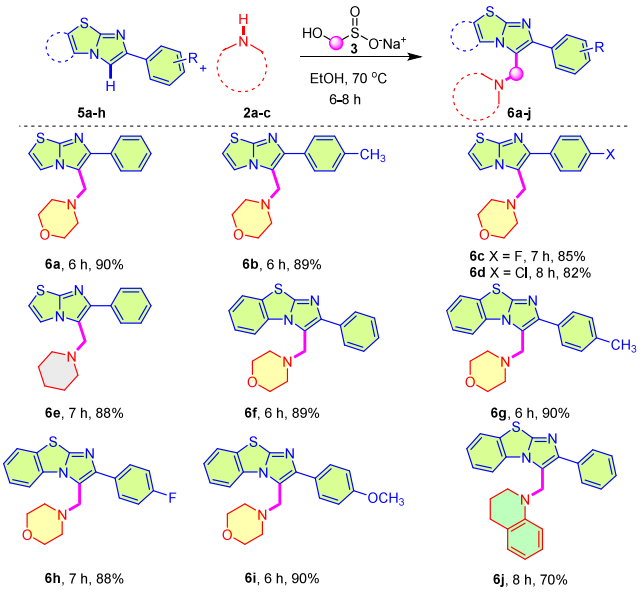
Scheme 2. One-Pot Aminomethylation of Imidazo[1,2-*a*]pyridine Derivatives[a,b]



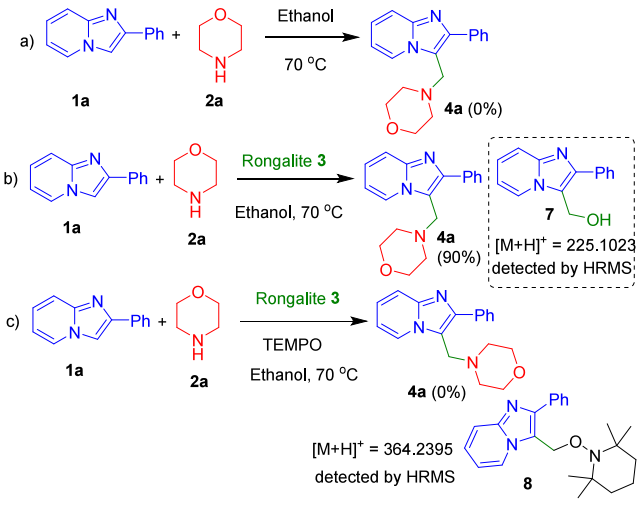
[a]All the reactions were conducted on a 1.0 mmol scale of **1a−o** (1.0 mmol), **2a−c** (1.0 mmol) and **3** (1.5 mmol) in solvent (2 mL), unless otherwise mentioned. [b]Isolated yields.

Scheme 3. Aminomethylation of Imidazo[2,1-*b*]thiazole Derivatives[a,b]



[a]All the reactions were conducted on a 1.0 mmol scale of **5a−h** (1.0 mmol), **2a−c** (1.0 mmol) and **3** (1.5 mmol) in solvent (2 mL), unless otherwise mentioned. [b]Isolated yields.

Scheme 4. Control Experiments



Finally, we have also tested our protocol on gram scale for the industrial applications with **4a** (1g) scale and obtained the product in 84% yield.

To gain mechanistic insight into one-pot aminomethylations, we conducted control experiments (Scheme 4). First, we carried out control experiments on imidazo[1,2-*a*]pyridine **1a** (1.0 mmol) and morpholine **2a** (1.0 mmol) in 2 mL of ethanol at 70 °C without rongalite **3** (Scheme 4a). However, this failed to produce target compound **4a**. This result indicates that C1 is sourced from rongalite. Next, we repeated the same reaction in the presence of rongalite (1.5 mmol) and recorded the HRMS of the samples at different intervals. These samples showed the formation of (2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanol **7** (Scheme 4b).

Finally, the aminomethylation reaction was conducted in the presence of TEMPO (3.0 mmol) in 2 mL of ethanol at 70 °C. No progress in the reaction was observed to provide **4a** (Scheme 4c). However, the formation of a TEMPO adduct with imidazo[1,2-*a*]pyridine **8** was observed when HRMS of the sample was recorded (Scheme 4c).

Based on the control experiments and previous literature reports,[5,7] a plausible mechanism is proposed in Scheme 5. Initially, the rongalite dissociated itself into formaldehyde and HSO_2^-. Later on, imidazo[1,2-*a*]pyridine **1a** reacts with *in situ* generated formaldehyde to obtain intermediate **7**. The intermediate **7** undergoes dehydration to yield the iminium ion **III**. Further, morpholine attacks the iminium ion to form intermediate **IV**, which further deprotonates to form the desired compound **4a**.

In summary, this study successfully demonstrates a one-pot aminomethylation strategy for imidazo[1,2-*a*]pyridine and heteroarenes using secondary amines/anilines and rongalite as an *in situ* C1 source. The method is efficient, providing high yields under mild conditions and offers a green alternative to traditional aminomethylation techniques. Rongalite's role as a nontoxic, easily handled formaldehyde equivalent enhances the

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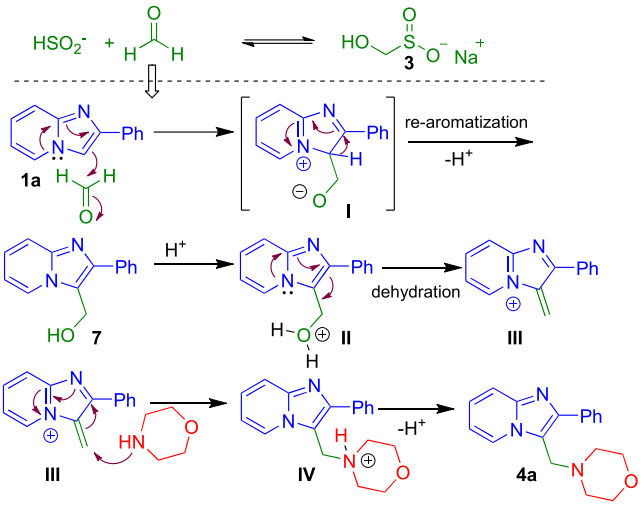
Scheme 5. Plausible Reaction Mechanism



method's practicality and environmental friendliness. This approach broadens the scope of aminomethylation in organic synthesis, paving the way for its application in pharmaceuticals.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c02050.

Experimental details, procedures, characterization data, and spectral data for all new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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