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Sort Communication

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Sommelet Reaction: A Novel Metal-Free Strategy in the Synthesis of Pyrimidine N-Oxides Compounds

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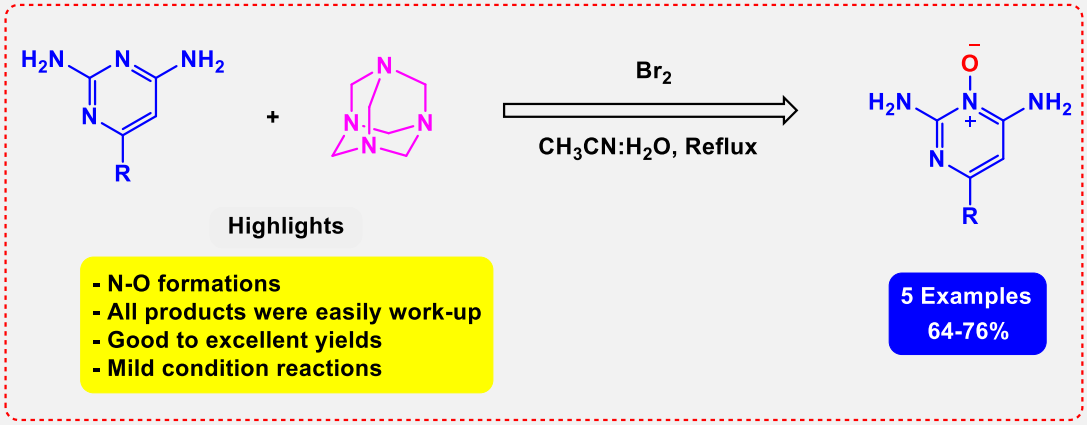
ABSTRACT: The main use of minoxidil, also known as 2,4-diamino-6-piperidinopyrimidine 3-oxide, is to lessen vascular resistance to blood flow. Later, it became known as a more significant medication for stimulating hair growth on the scalp, reversing baldness, and treating androgenic alopecia by boosting prostaglandin endoperoxide production. The synthesis of pyrimidine N-oxides using the proper carboxamide oximes is explained in general terms. Various pyrimidine N-Oxides must be treated in the presence of hexamethylenetetramine as a catalyst in order to convert them. The synthesis of Pyrimidine N-Oxides from Pyrimidine scaffolds catalyzed by Hexamethylenetetramine (HMA) was accomplished using an effective stray forward method. Pyrimidine N-Oxides were produced using a straightforward process employing Sommelet reaction oxidation with high yield. The HMA catalyzed system is affordable and suitable from an industrial standpoint.



KEYWORDS: Sommelet reaction, Pyrimidine N-Oxides, Br_2 molecular, Green system, Water.

■ Introduction

Simple nitrogen-containing heterocycles are given a lot of attention in the literature [1–4] for tiny chemical compounds and are prevalent in many different natural products. Minoxidil, a drug used to treat high blood pressure [5], and pattern hair loss, [6], are just a few examples of the many biologically active compounds that contain N-Oxide scaffolds. Numerous medications, biological agents, and organic compounds, such as otamixaban, ancriviroc, quindoxin, olaquindox, carbadox, chlordiazepoxide, are pharmaceutical N-Oxide drugs include the pyrimidine N-Oxides ring skeletons that are shown in **Figure 1**.

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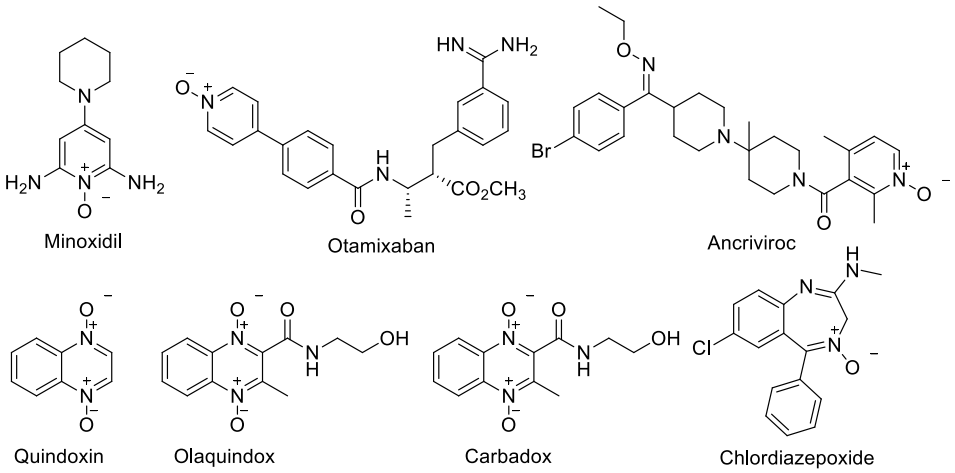
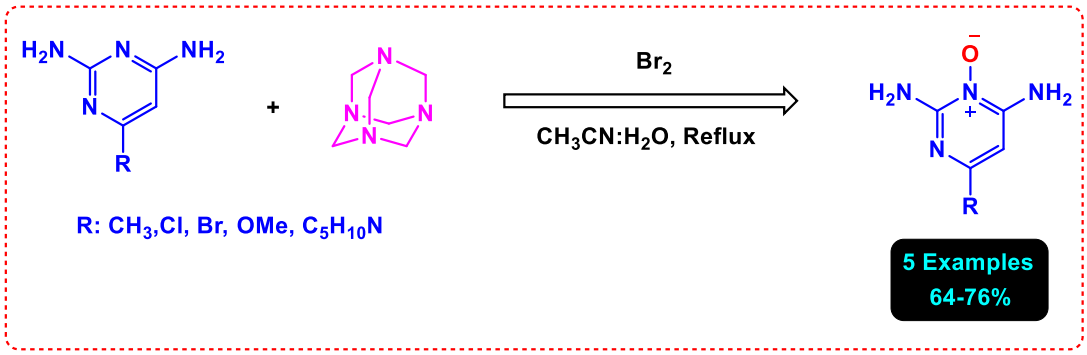


Figure 1. Several examples of pharmaceutical N-Oxide drugs.

Many naturally occurring substances and biologically useful chemicals contain pyrimidine N-oxides scaffolds. In addition to its use as anticoagulant [7], anti-HIV[8], anti-infection [9], Antimycobacterial [10], Antitumor [11], anxiety, insomnia, anticonvulsant, anxiolytic, hypnotic, sedative and skeletal muscle relaxant [12], pyrimidine N-oxides has a wide spectrum of pharmacological properties [13–15]. As a result, numerous techniques for making pyrimidine N-oxides have been documented in the literature throughout the years [16,17]. There are several synthetic pathways for the synthesis of pyrimidine N-oxides skeleton moieties in this regard, such as metal-Catalyzed Cross-Coupling [13], C–H Functionalization of Heterocyclic [18,19], Cyclic voltammetry [20] and Visible-Light-Mediated [21]. These inquiries are still in their early stages, though. We planned to study the reaction between 6-methylpyrimidine-2,4-diamine **(1a-e)**, bromine, HMA (**2)** and in this paper in the context of our research on the design and synthesis of nitrogen heterocyclic compounds. This research was motivated by these groundbreaking investigations. While this methodology has not yet been reported, a series of 2,6-diamino-4-methylpyrimidine-1-oxide derivatives **(3a-e)** were developed and created here (**Scheme 1**).



Scheme 1. Synthetic pathway for the formation of the 2,6-diamino-4-methylpyrimidine-1-oxide derivatives.

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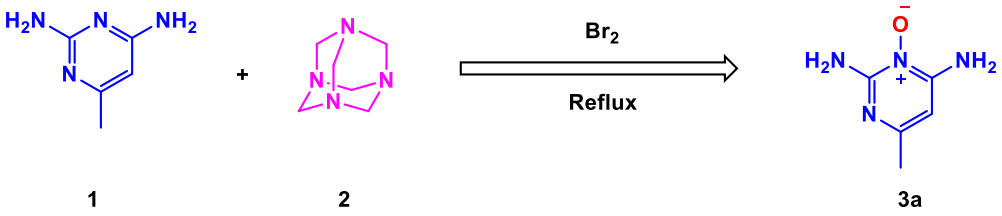
■ Result and discussion

6-Methylpyrimidine-2,4-diamine (**1a),** bromine and HMA (**2)** were initially selected as substrates to examine the reaction conditions. The type of catalyst was discovered to be crucial to the outcome of this synthesis (**Table 1**). first, the model reaction carries out at room temperature and reflux in EtOH, CH_3CN after 10h, and in this protocol no reaction took place in the absence of catalyst (**Table 1, Entry 1-4**). Therefore, we decided to change reaction condition. The model reaction was performed in the presence of, H_2O_2, HMA, and $KMnO_4$ as an oxidant agent at reflux (**Table 1, Entry 5-11**), surprisingly we observed different results. When the model reaction was performed in the presence of H_2O_2, HMA and $KMnO_4$ as an oxidant at reflux (**Table 1, Entry 5-6**), a satisfactory improvement in the isolated yield was observed in 3h. But the reaction desired product was separated in low isolated yield with maximum yield in HMA and CH_3CN after 3h.

Table 1. Optimization of the reaction conditions for synthesis of pyrimidine N-Oxides



1 2 3a

Entry	Solvent	Temp (°C)	Oxidant	Time (h)	Yield (%)
1	CH_3CN[a]	r.t	__	10	___
2	EtOH	r.t	__	10	___
3	CH_3CN	Reflux	__	10	___
4	EtOH	Reflux	__	10	___
5	CH_3CN	Reflux	H_2O_2	3	33
6	CH_3CN	Reflux	HMA	3	76[a]
7	CH_3CN	Reflux	$KMnO_4$	3	45
8	EtOH	Reflux	HMA	3	12

[a] CH_3CN 70%

Scheme 2 depicts a potential mechanism for the production of the pyrimidine N-Oxides derivatives **(3a-e).** Inspiring by this achievement, we created pyrimidine N-Oxides under comparable circumstances **Table 2**. Additionally, All Compounds **(3a-e)** derivatives were identified using elemental analysis, 1HNMR spectroscopy and melting point analysis.

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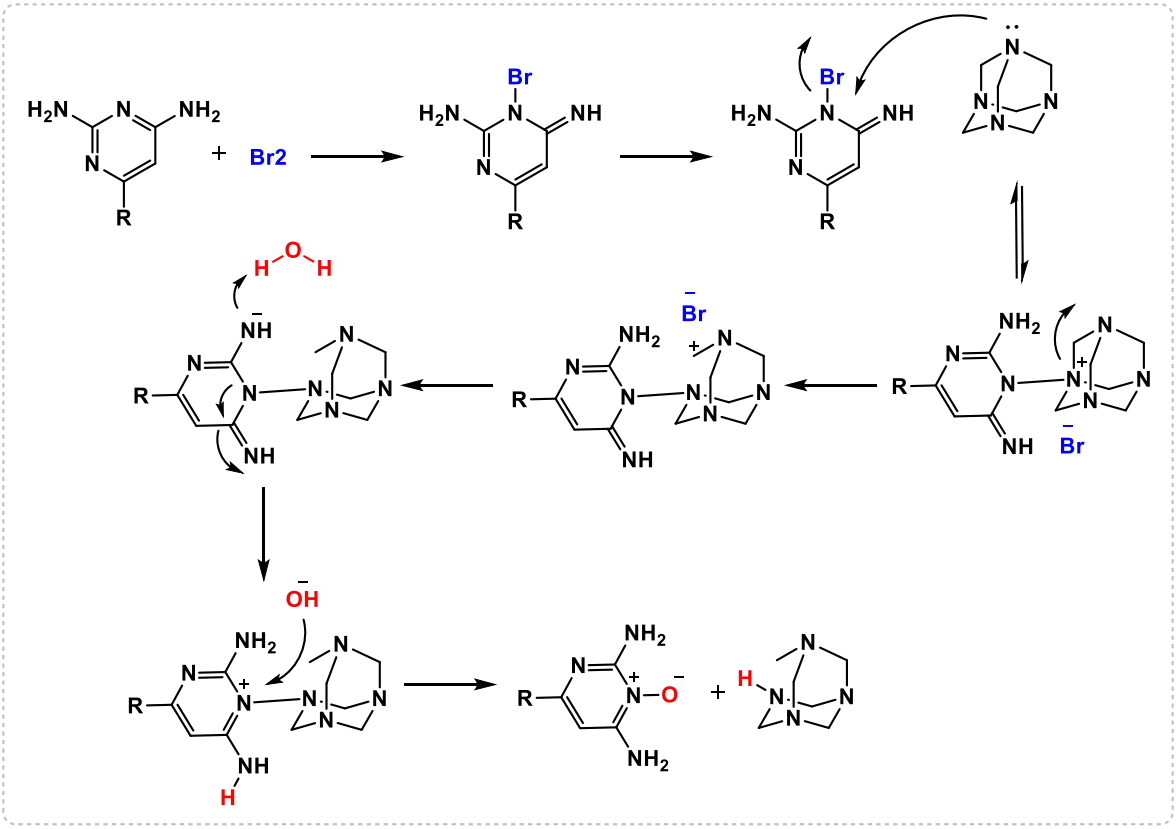

Scheme 2. Possible mechanism for the synthesis of pyrimidine N-Oxide derivatives.

Encouraged by this achievement, we envisioned that this strategy might be applied to the reaction of pyrimidine N-Oxides (**1**), bromine (**2**) and HMA (**3**), to develop a simpler, more efficiency and more reliable methodology for the synthesis of 2,6-diamino-4-methylpyrimidine-1-oxides **(4a-e)**. However, contrary to our expectation, under the same conditions (**Table 2**), when this reaction was carried out in CH_3CN the yield of the product was 54% (**Table 3, Entry 8**). After screening the solvents, it was being mentioned that high conversion was obtained by using CH_3CN as a solvent by using optimal reaction conditions (**Table 3, Entry 10**).

■ Summary and outlook

In summary, we have developed an excellent selective N-Oxidation reaction. This new process represents a viable approach for the syntheses of 2,6-diamino-4-methylpyrimidine-1-oxide compounds from the reaction of pyrimidine scaffolds with bromine oxidized by HMA as an inexpensive oxidant also environmentally friendly procedure in moderate to good yields.

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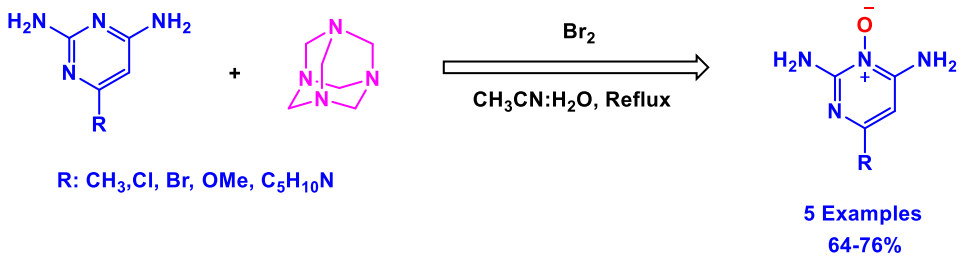
Table 2. Synthesis of 2,6-diamino-4-methylpyrimidine-1-oxide derivatives



Product	R_1	Time (h)	m.p (°C)	Yield %
3a	CH_3	3	221-224	76
3b	Cl	2	233-235	74
3c	Br	2	232-235	66
3d	OCH_3	2	240-243	64
3e	$C_5H_{10}N$	4	254-256	72

■ Experimental

All of the chemicals and solvents are commercially available and were purchased. All of the chemicals and solvents were bought off the market. Using Merck silica gel (70-230 mesh) plates, thin layer chromatography (TLC) was used to track the reactions' progress. HMA were created following techniques described in the literature [22,23]. On an Electro-thermal 9200 system, melting points were measured in open capillary tubes. On a Bruker 300 DRX Avance instrument, 1H NMR (300 MHz) spectra were determined. A Heraus CHN fast analyzer was used to conduct elemental studies for C, H, and N.

General Procedure for the preparation of compounds (3a-e).

A mixture of 6-Methylpyrimidine-2,4-diamine (**1a**, 1mmol) and bromine in CH_3CN/water (70:30) (5 mL) at room temperature for 1h and the reaction progress was monitored by TLC (Ethyl acetate: n-Hexane, 1:2), after completion of the reaction, hexamethylenetetramine (**2**, 1.1 mmol) was added to the reaction mixture and heated at reflux for 3h. The mixtures were stirred at room temperature for 30 min then reaction mixture was cooled to 10 °C. The resultant solid was filtered and recrystallization in EtOH: Water (2-1) to afford pure white solid crystals (Products).

2,6-diamino-4-(piperidin-1-yl)pyrimidine 1-oxide (minoxidil) (3a).
White solid, mp: 254-256°C, (mp: 258-260°C [16]), ^{1}H NMR (300 MHz, DMSO-d_6) δ_H (ppm) 6.71 (bs, 4H, $2NH_2$), 5.24 (s, 1H, Ar-H), 3.12 (t, J = 5 Hz, 4H, $2CH_2$), 1.56-1.63 (m, 6H, $3CH_2$). Anal Calcd for $C_9H_{15}N_5O$: C, 51.66; H, 7.23; N, 33.47; O, 7.65%. Found: C, 51.24; H, 7.11; N, 33.18%.

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