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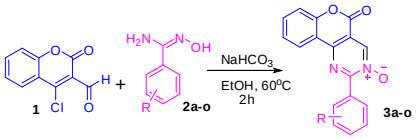

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ABSTRACT

A facile protocol for direct access to chromeno-pyrimidine-*N*-oxides is reported by the reaction of 4-chloro-3-formylcoumarin and aromatic carboximide oximes via tandem double nucleophilic addition and dehydration reactions. The one-pot reaction serves as an alternative protocol for achieving regioselective pyrimidine mono-*N*-oxide products as pure precipitates in good to excellent yields. The structure of the product was confirmed by X-ray analysis.

Pyrimidines are substructures of essential building blocks of nucleotides which make the composition of DNA and RNA. Their wide range of applications in medicinal chemistry make them a class of highly admired privileged structures.[1] Derivatives of pyrimidines such as pyrimidine-*N*-oxides are versatile class of compounds which like their precursors have gained ample importance in recent years. A well known pyrimidine-*N*-oxide, Minoxidil is an efficient vasodilator and anti-hypertensive molecule.[2] It is popularly used to treat the male baldness associated with androgenic or androgenetic alopecia.[3] Additionally, they account for potential applications as growth regulators and herbicides.[4] Apart from biological applications pyrimidine-*N*-oxides are employed as intermediates for the synthesis of several heterocyclic scaffolds.[5]

Most familiar straightforward approach to access pyrimidine-*N*-oxides is *N*-oxidation of pyrimidines with hydrogen peroxide.[6] Organic peracids and their complexes have also been used successfully for the *N*-oxidation of pyrimidines.[7] However, unlike pyridines, the *N*-oxidation of pyrimidines is relatively complicated as the reaction is susceptible to low yields due to ring-carbon oxidation, ring opening reactions and formation of isomeric products.[8] Alternative methods other than direct *N*-oxidation of pyrimidines have also been developed which employ ring closure, ring transformations and substitution reactions of a variety of starting materials to access the pyrimidine-*N*-oxides.[9] One of the simple methods for generation of pyrimidine-*N*-oxides was achieved by reaction of carboxamide oximes with active methylene 1,3-dicarbonyl compounds in presence of Lewis acids.[10] Similar synthesis of trifluoromethylated pyridine-*N*-oxides was achieved by reaction of 3-amino-5-methyl-1,2,4-oxadiazoles and 1,2-diketones under perchloric acid conditions *albeit* in poor yields.[11] Imidazole aminooximes and orthoformates were successfully exploited as precursors to afford purine mono-*N*-oxides.[12] Ring rearrangement of oxadiazolyl-enamino ketones[13] and DBU catalyzed reaction of nitroarenes with ethyl isocyanoacetates[14] were also reported as elegant methodologies to access the privileged *N*-oxide compounds. However most of the methods suffer either from limited substrate scope, poor yields or employs high temperatures up to 200 °C to achieve the target molecules.

Application of tandem methodologies has witnessed enormous surge in recent times for the generation of several complex heterocyclic molecular targets of biological interest.[15] This would be a highly attractive approach where synthesis of pyrimidine-*N*-oxides can be accomplished using easily accessible starting materials which evade the disadvantages of isolation of the intermediates and generation of waste solvents. We have earlier reported the synthesis of novel 2-benzazepines via tandem nucleophilic reaction and cyclization using 4-chloro-3-formylcoumarin **(1)** and aromatic benzylamines.[16] Herein, we envisaged a facile protocol for direct generation of novel fused chromeno-pyrimidine-*N*-oxides by a reaction of **1** with aromatic carboxamide oximes **2a-o**. For the initial validation of the protocol and the optimization of the reaction conditions, **1** was

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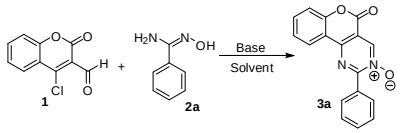
subjected to the reaction with *N'*-hydroxybenzimdamide **2a** under various base catalyzed conditions in different solvents (Table 1).

Table 1. Screening studies of the reaction of **1** and **2a** with various bases and solvents[a].



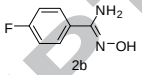
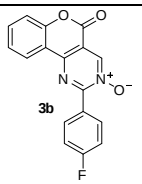
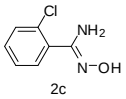
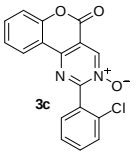
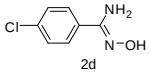
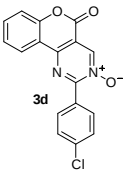
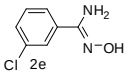
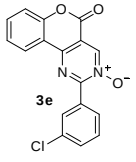
Entry	Base	Solvent	T (°C)	Time(h)	Yield (%)[b]
1	NEt_3	EtOH	rt	24	30
2	NEt_3	EtOH	60	12	50
3	DBU	EtOH	60	2	40
4	DABCO	EtOH	60	2	40
5	DIPEA	EtOH	60	2	56
6	$NaHCO_3$	EtOH	60	2	85[c]
7	$NaHCO_3$	MeOH	60	2	70
8	$NaHCO_3$	DCM	reflux	2	30
9	$NaHCO_3$	$CHCl_3$	reflux	2	25
10	$NaHCO_3$	THF	60	2	20
11	$NaHCO_3$	1,4-dioxane	60	2	40

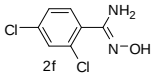
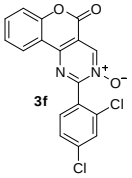
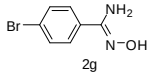
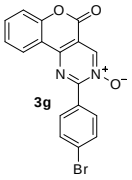
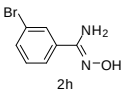
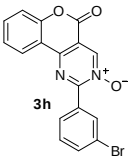
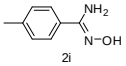
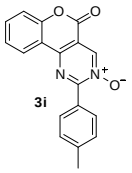
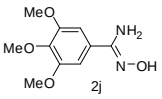
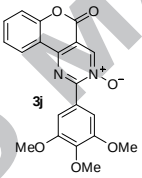
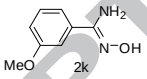
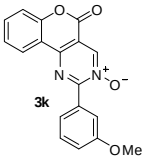
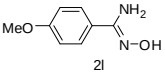
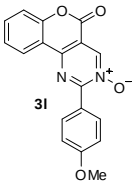
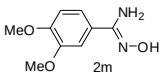
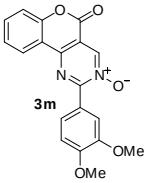
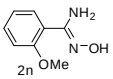
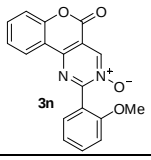
[a]All the reactions were performed on 1 mmol scale with 1 equiv. of base in 5 ml solvent.
[b]isolated yields.
[c]precipitated yield.

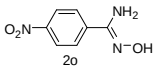
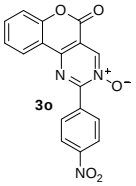
As illustrated in Table 1, to identify the best base for the reaction of **1** and **2a**, various bases such as NEt_3, DBU, DABCO, DIPEA and sodium bicarbonate were employed as promoters in ethanol solvent. When triethylamine was employed as base in ethanol at room temperature the reaction afforded pyrimidine-*N*-oxide **3a** in 30% yield which improved to 50% when temperature was raised to 60 °C (Table 1, entries 1 and 2). All further optimizations were conducted at this temperature. While DBU, DABCO and DIPEA afforded the product **3a** in 40-56% (Table 1, entries 3-5) yields, sodium bicarbonate gave best yield of 85% (Table 1, entry 6) in 2 hours. Similarly, the choice of solvent also displayed profound effect on the reaction yields where solvents such as methanol, dichloromethane, chloroform, THF and 1,4-dioxane afforded 20-70% yields of **3a** (Table 1, entries 7-10). From the observations of the optimization studies in Table 1, it can be surmised that sodium bicarbonate afforded the best yield of product **3a** in ethanol solvent and hence all further experiments were conducted with this system.

The optimized reaction conditions were further utilized to evaluate the substrate scope of the reaction. Diverse carboxamide oxime substrates **2b-o** as shown in Table 2 were thus assessed for their reactivity under the experimental conditions. When the carboxamide oximes with halogen substituents such as 4-F, 2-Cl, 4-Cl, 3-Cl, 2,4-dicloro, 4-Br and 3-Br (Table 2, entries 1-7) were subjected to the reaction with **1**, corresponding pyrimidine-*N*-oxides were obtained in good to excellent yields (75-85%). Similarly, carboxamide oximes **2i-n** possessing electron donating functional groups such as 4-methyl, 3,4,5-trimethoxy, 3-methoxy, 4-methoxy, 3,4-dimethoxy, and 2-methoxy substituents also afforded the corresponding products **3i-n** in good to excellent yields (Table 2, entries 8-13). However, in case of electron withdrawing 4-nitro substrate **3o**, the reaction afforded only *N*-alkylated product despite prolonged reaction times. Hence a reaction was attempted in 1,4-dioxane solvent with the intention of attaining higher reaction temperatures. To our delight, the required pyrimidine-*N*-oxide **3o** was afforded in 65% yield after 3 hours of reflux (Table 2, entry 14). Attempts to expand the scope of the reaction to aliphatic substrates did not yield fruitful results, as the reaction resulted in mixture of several unidentified products due to the relative instability of the aliphatic carboxamide oximes under the experimental conditions.

Table 2. Synthesis of diverse chromeno-pyrimidine-*N*-oxides **3b-o**[a]

Entry	Substrate (2b-p)	Product (3b-p)	Yield (%)[b]
1			77
2			75
3			82
4			75

5	 2f	 3f	80
6	 2g	 3g	77
7	 2h	 3h	85
8	 2i	 3i	82
9	 2j	 3j	88
10	 2k	 3k	80
11	 2l	 3l	78
12	 2m	 3m	85
13	 2n	 3n	75

14	 2o	 3o	65[c]

[a]All the reactions were performed on 1 mmol scale with 1 equiv. of $NaHCO_3$ in 5 ml ethanol at 60°C.
[b]Precipitated yields.
[c]Reaction performed in 1,4-dioxane under reflux condition

The structure of the product was confirmed by X-ray analysis of **3d** as shown in Figure 1. The molecule was crystallized in monoclinic system with space group *C 2/c* with eight molecules in the unit cell. The crystal is stabilized by C−H···O⁻, C−H···O and C−H···Cl interactions. The chloro benzene ring is tilted by 12.8° away from the plane of the pyrimidine-*N*-oxide moiety (Also refer crystal data and crystal packing diagram in supplementary data).

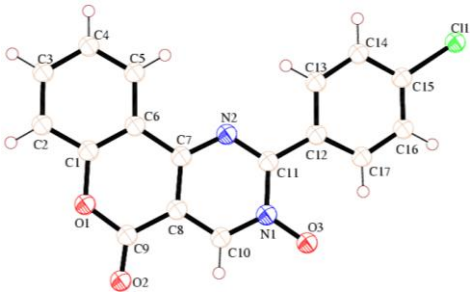
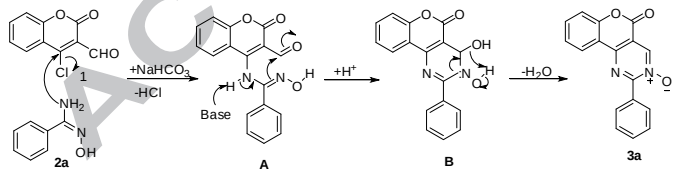


Fig. 1. ORTEP plot for the X-ray crystal structure of **3d** at 30% probability.

In all the above reactions (Table 2, entries 1-14) a precipitate was observed after initial 15 minutes of reaction which re-dissolves and re-precipitates to afford products **3a-o**. The first precipitated solid was isolated in the reaction of **2a** with **1** and confirmed as *N*-alkylated intermediate **A** of primary amine (Scheme 1). Based on the above observations, mechanism as shown in Scheme 1 can be proposed where the initial nucleophlic addition of the primary amine on **1** leads to an *N*-alkylated Intermediate **A.** Intermediate **A** further undergoes a base catalyzed deprotonation triggering the nucleophilic addition of the oxime amine on the aldehyde resulting in intermediate **B**, which subsequently undergoes dehydration leading to the final chromeno-pyrimidine-*N*-oxide **3a**.



Scheme 1. Mechanism for the formation of **3a** intermediate **A**.

In summary, we have reported a facile protocol for direct access to novel chromeno-pyrimidine-*N*-oxides via tandem double nucleophilic addition and dehydration steps. The reaction offers a complementary approach for obtaining selective mono-*N*-oxides products of pyrimidines in good yields. Additionally, all the products were afforded as pure precipitates avoiding the necessity for tedious column purification steps. Further investigations on structural diversification and biological implications of the structural scaffolds are currently being conducted.

Acknowledgments

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Supplementary data

General experimental section, analytical data for compounds **3a-o** and the X-ray analysis of **3d** can be found in supplementary data. Crystallographic data of **3d** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 902947. The data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

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Graphical Abstract

Direct access to novel chromeno-pyrimidine-*N*-oxides via base catalyzed tandem double nucleophilic addition/dehydration reaction

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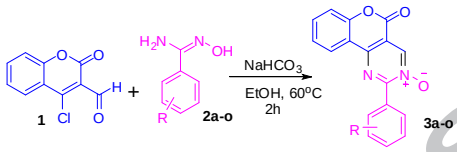

Abstract: A facile protocol for direct access to chromeno-pyrimidine-*N*-oxides is reported by the reaction of 4-chloro-3-formylcoumarin and aromatic carboximide oximes via tandem double nucleophilic addition and dehydration reactions. The one-pot reaction serves as an alternative protocol for achieving regioselective pyrimidine mono-*N*-oxide products as pure precipitates in good to excellent yields. The structure of the product was confirmed by X-ray analysis.