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Condensation of Vilsmeier Salts, Derived from Tetraalkylureas, with α- Hydroxy Amides Derivatives: One-pot Approach to Synthesize 2-Dialkylamino-2-oxazolin-4-ones

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Condensation of Vilsmeier Salts, Derived from Tetraalkylureas, with α- Hydroxy Amides Derivatives: One-pot Approach to Synthesize 2-Dialkylamino-2-oxazolin-4-ones

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A novel and straightforward synthetic protocol was developed to synthesize 2-dialkylamino-2-oxazolin-4-ones from various Vilsmeier salts and α-hydroxy amides derivatives. Notablely, Thozalinone (**3a**) as a mild stimulant on tristimania and anorexic, could be synthesized simply and in a high yield using this methodology.

2-Oxazolin-4-ones are one of the most important privileged skeletons in diverse pharmaceutically active molecules and natural products.[1-9] For example, Hecker synthesized antimicrobial nature product, (±)-indolmycin, and Mills discovered a pharmaceutical molecule, hydroisoindolin 3 (Figure 1).[7, 10] Due to their potential biological activities, compounds, 2-oxazolin-4-ones, have been extensively focused on by a growing number of organic chemists.[11-17] In 1958, 2-amino-2-oxazolin-4-ones have been reported detailedly about its pharmacological activity.[13] Subsequently, it has been indicated that 2-dimethylamino-5-phenyl-2-oxazolin-4-one has an effect on tristimania and anorexia.[18]

In the past half century, a lot of methodologies with regard to the synthesis of 2-oxazolin-4-one derivatives have been explored,[4, 9, 18-24] however, reports relative to synthesis of 2-dialkylamino-2-oxazolin-4-ones are limited. For example, Traube used mandelic ester and guanidine to synthesize 2-amine-5-phenyl-2-oxazolin-4-one in 90% yield (Figure 2, a).[22] Howell reported that 2-dimethylamino-5-phenyl-2-oxazolin-4-ones were synthesized under reflux by performing the reaction of ethyl mandelate with dimethylcyanamide in a benzene solution**.** The reaction was accelerated by adding a certain amount of sodium hydride, the objective product was isolated in low yield (Figure 2, b).[18] However, one of the ultimate difficulties in these methods is the possibility to obtain 2-dialkylamino-2-oxazolin-4-ones scaffold in a high yield under mild conditions. In this context, developing a novel, effective and straightforward methodology of constructing 2-dialkylamino-2-oxazolin-4-ones scaffold is still desirable.

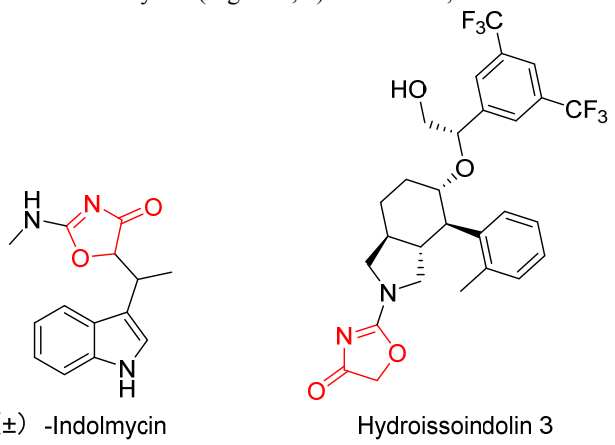


Figure 1. Examples of pharmaceutical molecules with a 2-oxazolin- 4-ones core structure

In our previous works, we have developed a methodology to obtain heterocyclic compounds with Vilsmeier salts.[25] In continuation of our studies on constructing heterocyclic compounds using Vilsmeier salts as synthons, herein, we would like to report a novel and straightforward strategy to synthesize 2-dialkylamino-2-oxazolin-4-ones derivatives from α-hydroxy amides[26-35] and Vilsmeier salts[36] by one-pot reaction (Figure 2, c). To the best of our knowledge, this methodology is unprecedent.

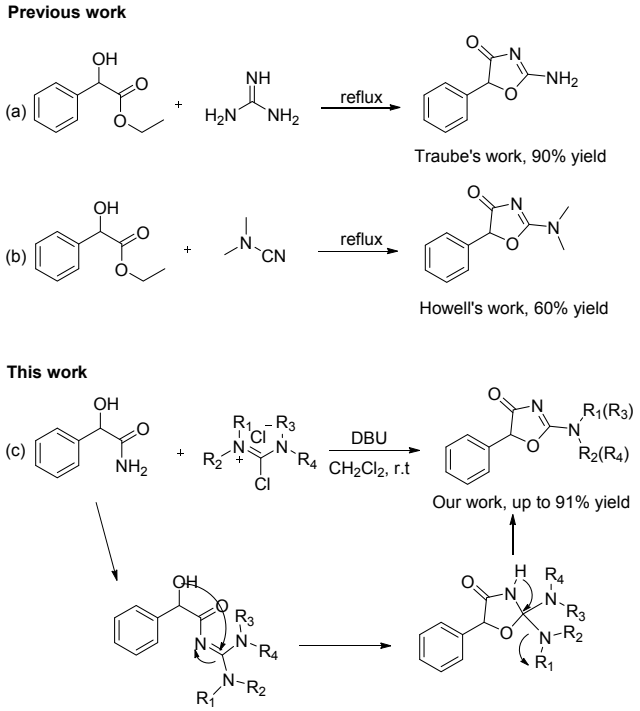
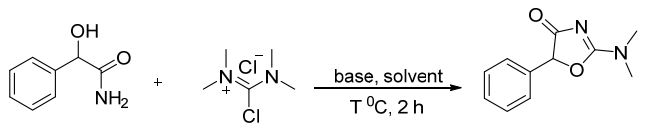


Figure 2. Synthesis of 2-amino-2-oxazolin-4-ones skeleton

Initially, we selected mandelamide (**1a**) and N,N,N',N'-tetramethylchloroformamidinium chloride (**2a**) as model substrates to screen out the privileged conditions for this one-pot reaction. The experiment was performed with 2 equiv of DIPEA, using mandelamide (**1a**) (1 mmol) and **2a** (2 mmol) and 10 ml acetone at room temperature for 2 h. As shown in Table 1, only trace amount of product **3a** was obtained under

above reaction conditions (Table 1, entry 1), subsequently, we replaced acetone with chloroform, DCM and acetonitrile,

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	**1a**:**2a**	Base (equiv)	Solvent	T (℃)	Yield[b] (%)
1	1:2	DIPEA (2)	Acetone	25	Trace
2	1:2	DIPEA (2)	$CHCl_3$	25	33
3	1:2	DIPEA (2)	DCM	25	35
4	1:2	DIPEA (2)	Acetonitrile	25	27
5	1:2	DMAP (2)	DCM	25	42
6	1:2	Et_3N (2)	DCM	25	58
7	1:2	DBU(2)	DCM	25	63
8	1:2	DBU (4)	DCM	25	72
9	1:2.5	DBU (4)	DCM	25	88
10	1:1.5	DBU (4)	DCM	25	60
11	1:2.5	DBU (4.5)	DCM	25	85
12	1:2.5	DBU (3)	DCM	25	82
13	1:2.5	DBU (2)	DCM	25	74
14	1:2.5	DBU (4)	DCM	30	84
15	1:2.5	DBU (4)	DCM	45	82

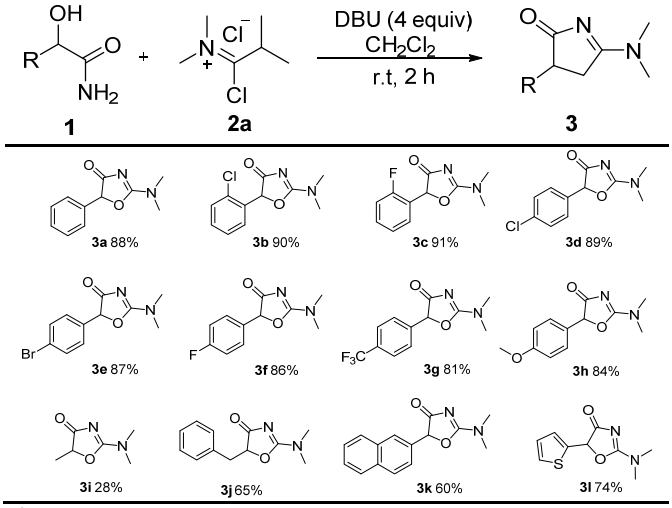
[a]Reactions were conducted at 1 mmol scale in 10 ml of solvent, the conversions were determined by TLC. [b]Isolated yields.

respectively, then we found that solvents have an important effect on the one-pot reaction (Table 1, entries 2-4); as we have seen, product **3a** was obtained in 35% yield (Table 1, entry 3) when DCM was used.

Next, we examined the effect of different bases, such as DMAP, Et_3N and DBU on the reaction (Table 1, entries 5-7), and ultimately, we used 4 equiv of DBU and got 2-dialkylamino-5-phenyl-2-oxazolin-4-ones in 72% yield (Table 1, entry 8). Gratifyingly, the reaction gave a promising result of 88% yield when the amount of **2a** was increased to 2.5 equiv (Table 1, entry 9). However, 1.5 equiv of **2a** was added, the yield of **3a** was decreased to 60% yield （Table 1, entries 10）. With the amount of DBU increased or decreased, yields of **3a** had no obvious changes (Table 1, entries 11 and 12). However, when the amount of DBU was reduced to 2 equiv the yield of **3a** has a alter obviously. In the end, we intended to improve the yield by regulating the temperature, and the results show that the temperature is not the main factor in this one-step reaction (Table 1, entries 14 and 15). After screening different reaction parameters, the optimal reaction conditions were as follows: **1a**:**2a**(mole ratio)=1:2.5, CH_2Cl_2 as solvent, 4 equiv of DBU as a base, and stirred at room temperature for 2 h.

After the optimized conditions were established, a series of α-hydroxy amides (**1**) were selected to react with N,N,N',N'-tetramethylchloroformamidinium chloride (**2a**), and corresponding products were obtained in moderate to excellent yields (up to 91% yield). As shown in Table 2, substrates including electron-donating groups or electron-withdrawing groups in *para*-position of the phenyl ring (such as 4-Cl, 4-Br, 4-F, 4-CF_3, 4-OCH_3, Table 2, entries 4-8) were amenable, and the corresponding products were obtained in high to excellent isolated yields (Table 2, entries 4-8, 81%-89% yields). Significantly, a pharmaceutical activity compound **3a** was easily synthesized with **1a** and **2a** in 88% isolated yield; apparently, this method is efficient and straightforward compared with Howell's work (in 60% yield). Dramatically, substrates **1b** and **1c**, in which *ortho*-position substituents of the phenyl ring are 2-Cl and 2-F, respectively, generated corresponding products **3b** and **3c** in 90% and 91% isolated yields (Table 2, entries 2 and 3), respectively. Moreover, the reaction substrates were extended to α-aliphatic hydroxy amides **1i** and **1j**, the corresponding products **3i** and **3j** were obtained in 28% and 65% isolated yields (Table 2, entries 9 and 10), respectively. In order to prove the generality of this synthetic method, condensed ring napthyl- and heteroaromatic ring thienyl- substituted α-hydroxy amides **1k** and **1l** were subjected to the reaction conditions, they were well-tolerated and successfully gave objective products **3k** and **3i** in 60% and 74% isolated yields (Table 2, entries 11 and 12).

Table 2. Substrate scope of the α-hydroxy amides.[a]

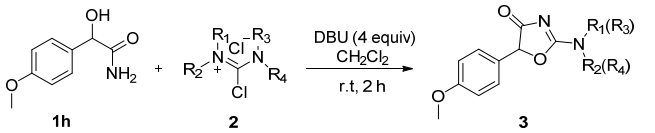


1 **2a** **3**

[a]Reactions were conducted at 1 mmol scale in 10 ml of solvent

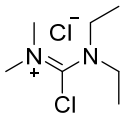
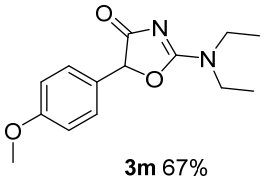
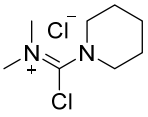
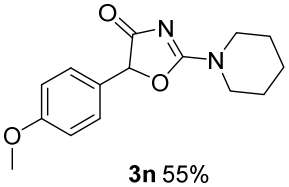
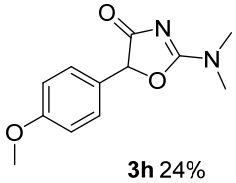
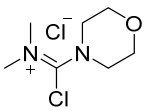
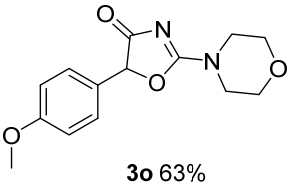
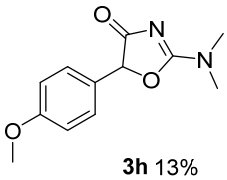
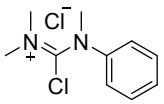
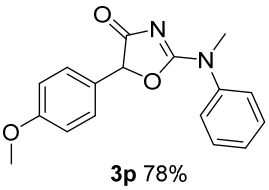
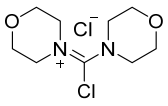
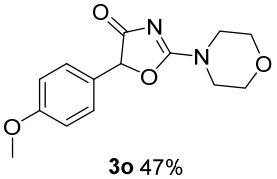
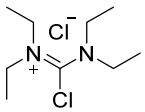
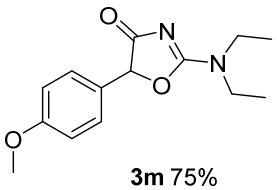
Next, a various of Vilsmeier salts including symmetric and asymmetric substituents were explored in the reaction with 4-methoxymandelamide (**1h**) and the results were listed in Table 3. As shown in Table 3, in most cases, two products were obtained using asymmetric Vilsmeier **s**alts (Table 3, entries 2 and 3), while one of them was mainly obtained selectively, such as **3m** and **3p** (Table 3, entries 1 and 4). In addition, symmetric Vilsmeier salts **2f** and **2g** have been examined at the same time; as we have seen, product **3m** was obtained in 75% yield (Table 3, entry 6), however product **3o** was obtained in a relatively low yield (Table 3, entry 5) propably due to the steric hindrance of **2f**.

Table 3. Substrate scope of the Vilsmeier salts.[a]



1h **2** **3**

Entry	Substrate (**2b-2g**)	Product, Yield (%)[b]

1	 **2b**	 **3m** 67% Obtained as mainly product
2[c]	 **2c**	 **3n** 55%  **3h** 24%
3[c]	 **2d**	 **3o** 63%  **3h** 13%
4	 **2e**	 **3p** 78% Obtained as mainly product
5	 **2f**	 **3o** 47%
6	 **2g**	 **3m** 75%

[a] Reactions were conducted at 1 mmol scale in 10 ml of solvent. [b] Isolated yield. [c]Obtained double products.

In our previous work, we have explored the possible mechanism of the one-pot reaction. Under our optimized conditions, **1** and **2a** similarly experienced a nucleophilic substitution process and generated a guanidine intermediate. Subsequently, a intramolecular cyclization of the guanidine intermediate have taken place and the product **3** was formed (For details of the mechanism, see the Supporting Information).

In summary, we have developed a novel and straightforward methodology for synthesizing 2-dialkylamino-2-oxazolin-4-ones by one-pot reaction. Various Vilsmeier salts and α-hydroxy amides derivatives were investigated, and a series of corresponding products were obtained in good yields and a certain degree of selectivity. It's worth mentioning that we obtained a pharmacologically active compound **3a** in 88% yield by this methodology, and the pharmaceutical activity of products, analogous of **3a,** are being estimated in our laboratory.

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