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Unexpected route for the synthesis of *N*,*N*-dialkyl formamidines using phenyl chloroformate and *N*,*N*-dialkyl formamides

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ABSTRACT

An unexpected route for the synthesis of *N*,*N*-dialkyl formamidines has been reported by the reaction of amines with *N*,*N*-dialkyl formamides and phenyl chloroformate.

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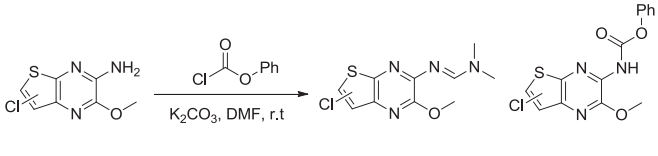
1. Introduction

Formamidines are the key intermediates for the construction of heterocycles[1] and functional group transformations.[2] They have also been employed as pharmacological agents,[3] protecting groups for primary amines,[4] and as a support linker in solid phase synthesis.[5] The use of formamidines as chiral auxiliaries in asymmetric synthesis[6] and as ligand for metal-catalyzed hydrosilylation and epoxidation has also been reported.[7] The methods for the synthesis of formamidines can largely be divided into three categories. The first involves the use of *N*,*N*-dialkyl formamide dialkylacetals with or without a catalytic amount of acid. The second involves coupling agents, such as $POCl_3$, P_2O_5, PCl_5, $(COCl)_2$, $SOCl_2$, acid chlorides, sulfonylchlorides, PyBOP, and trifluoroacetic anhydride.[8] The last involves the use of isolated iminium salt like vilsmeier reagent, which is related to the method of this report.[9] Recently, a new approach using NaI and TBHP to make *N*-sulfonyl formamidine has been reported.[10] As a part of our medicinal chemistry research program we required carbamate **3**, for which we attempted the reaction of phenyl chloroformate with amine **1** (Scheme 1). It was expected that the nucleophilic substitution would lead to the carbamate. However the product obtained was confirmed as formamidine **2**, strongly suggesting the formation of a reactive intermediate between *N*,*N*-dimethylformamide and phenyl chloroformate, which was reacting with amines (Scheme 2). These findings have not been reported, and have encouraged us to investigate the formamidine synthesis.

2. Results and discussion

We initially selected 3-aminopyridine and aminopyrazine to study the optimal conditions. The reaction proceeded well, but extraction with EtOAc was difficult due to its good solubility in water. To solve the problem, we used 6-chloro-2-aminopyrazine as a model substrate since it is well extracted with EtOAc. After selecting a model compound, we investigated the necessity of K_2CO_3 in the methodology and found that K_2CO_3 was not necessary for the reaction (Table 1, entries 1–4). Instead, the reaction required more phenyl chloroformate for completion. In the absence of the base, the product can be obtained as HCl salt via simple filtration, which makes the purification much easier. Two other chloroformates were also screened to compare their reactivity. Among the chloroformates (Table 1, entries 4 and 5), *p*-nitrophenyl chloroformate was found to show similar results to that of phenyl



1 2 3

Scheme 1.

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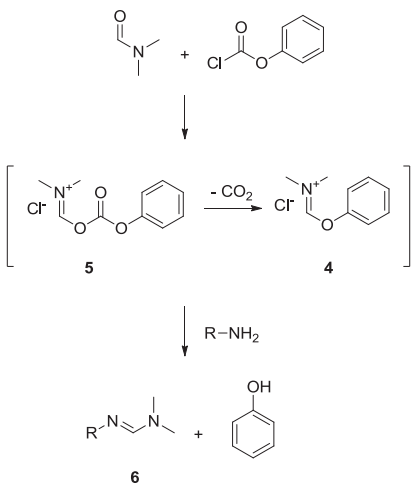
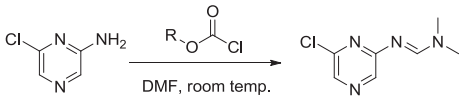
chloroformate, but ethyl chloroformate gave poor yields. Considering the price of the two aryl chloroformates, phenyl chloroformate was found to be the reagent of choice for the reaction.



Scheme 2.

Table 1
Reaction condition screening[a]



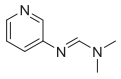
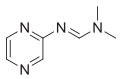
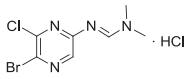
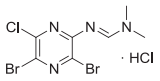
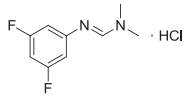
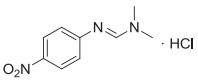
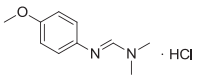
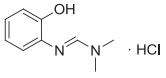
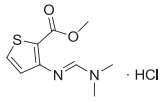
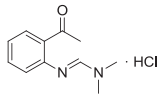
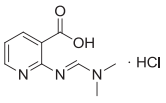
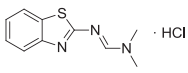
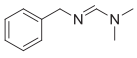
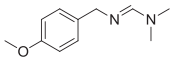
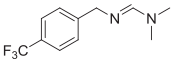
Entry	Base [equiv.]	R [equiv]	Time [min]	Yield[b] [%]
1	K_2CO_3 (2.7)	Ph (2.0)	5	79
2	K_2CO_3 (3.0)	Ph (2.2)	5	85
3	—	Ph (2.0)	5	86[c]
4[d]	—	Ph (2.0)	5	84[c]
5	—	Et (2.0)	5	12
6[e]	—	*p*-NitroPh (2.0)	5	84

[a] Reaction conditions: DMF (1 ml) and chloroformate were stirred for 5 min with base or not before addition of the 6-chloro-2-aminopyraizne (1 mmol).
[b] Isolated yield.
[c] Obtained as HCl salt.
[d] DMF (0.5 ml).
[e] DMF (2 ml).

To study the reaction details, DMF and phenyl chloroformate were mixed (1:1 molar ratio) and stirred for 5 min, and diluted into $CDCl_3$. The ^1H NMR spectrum indicated the existence of iminium salt, and that the DMF was completely consumed. However we were unable to confirm the intermediacy of either **4** or **5** because bubbles, suspected as CO_2 were observed in the mixture while stirring. A literature survey revealed the isolation of an iminium salt **4**, which is used as a chlorinating agent.[11] We also can isolate the intermediate **4** from the described procedure. It was thus concluded that the intermediate **5** formed initially underwent decarboxylation to form the intermediate **4**. The isolation of the intermediate **4** answers the formation of the formamidines (Scheme 2).

We started to explore the scope and limitations of the method (Table 2). It was found that a greater equivalent of the phenyl chloroformate has to be used as the nucleophilicity of amines decreases (Table 2, entries 1–4). In the case of trihaloaminopyrazine (Table 2, entry 4), the reaction worked well but the product could not be obtained due to its instability, both in the protic solvent and in the air. It easily turned back to the amine. Nitro, methoxy, hydroxy, methyl ester, carboxylic acid, and acetyl-substituted aryls also gave the desired products (Table 2, entries 6–11). When methyl 3-amino-2-thiophenecarboxylate was tested (Table 2, entry 9), the product was not generated as salt. So, we employed a silica gel column after aqueous work-up. However, we failed to obtain the

Table 2
Scope of the method[a]

Entry	Product		Time [min]	Yield[b] [%]
1[c]		**6b**	5	81
2[c]		**6c**	5	87
3[d]		**6d**	20	71
4[e]		**6e**	20	—
5		**6f**	5	87
6		**6g**	5	95
7		**6h**	5	79
8		**6i**	5	70
9		**6j**	5	90
10		**6k**	5	59
11		**6l**	10	60
12		**6m**	10	86
13		**6n**	5	50
14		**6o**	5	40
15		**6p**	10	59

[a] Reaction conditions: DMF (1 ml) and phenyl chloroformate (2 equiv) were stirred for 5 min at rt before addition of the amines (1 mmol).
[b] Isolated yield.
[c] Phenyl chloroformate (1.5 equiv) was used.
[d] 4.5 equiv of phenyl chloroformate.
[e] 7 equiv of phenyl chloroformate.

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