Tetrahedron 66 (2010) 1208–1214

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient access to polysubstituted amidines, benzimidazoles and pyrimidines from amides

Jing Wang [a], Zhenxing He [a], Xiaopeng Chen [a], Wangze Song [a], Ping Lu [a,*], Yanguang Wang [a,b,*]

[a] Department of Chemistry, Zhejiang University, Zheda Road 38#, Hangzhou, Zhejiang Province 310027, China
[b] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

ARTICLE INFO

Article history:
Received 17 October 2009
Received in revised form
7 December 2009
Accepted 11 December 2009
Available online 16 December 2009

Keywords:
Amides
Amidines
Benzimidazoles
Pyrimidines
Electrophilic activation

ABSTRACT

Polysubstituted amidines, benzimidazoles and pyrimidines were synthesized via the electrophilic activation of amides with trifluoromethanesulfonic anhydride and 2-chloropyridine. The one-pot protocol is concise and efficient and the substrates are readily available.

1. Introduction

Amidines are an important class of compounds for their biological properties[1] and applications in heterocyclic synthesis.[2] Consequently, their synthesis has received much attention.[3] Conventional methods for the preparation of polysubstituted amidines include imidoylation of amines with imidoyl chlorides,[4] imidate fluoroborates,[5] iminium triflates,[6] iminium sulfonates,[7] or imidoylbenzotriazoles.[3b]

As previous reported, amide is attractive starting material due to their easily accessible. However, amide itself is seldom used in organic synthesis for its relative stable. The nitrogen atom of the amide donates its lone pair electrons to C–N bond, both nucleophilicity of nitrogen and electrophilicity of carbonyl are hence decreased. There are several ways to activate the amide functional group in the literature. Among those methods, combination of trifluoromethanesulfonic anhydride (Tf_2O) and pyridine or 2-chloropyridine (2-ClPy) is hitherto the most attractive and feasible way. In the presence of a suitable nucleophile, a variety of compounds such as piperidines,[8] carboxylic acid derivatives,[9] amines,[10] pyrimidines,[11] and pyridines[12] were thus constructed via this electrophilic activation of amide pathway. Recently, we also developed a one-pot domino synthesis of indoles from amides and diazoacetate through finely tuning the electrophilicity of the activated *N*-aryl amides using the combination of Tf_2O, 2-ClPy and 2,6-Cl_2Py in a certain ratio.[13] As the extension of these preliminary results, we considered the amide itself function as a weak nucleophile and tested the possibility of the self-dimerization of amides. We herein report the details of this effort.

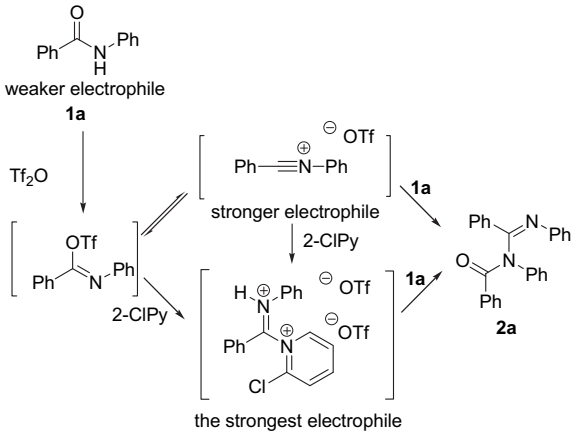
2. Results and discussion

Initially, we chose to focus our attention on the reaction of *N*-phenylbenzamide (**1a**). As we expected, when the combination of Tf_2O and 2-ClPy was used as the activating reagent, the amidine **2a** was readily obtained (Scheme 1).

In order to obtain the optimized reaction conditions, several combinations of base additive were investigated (Table 1). When pyridine and its analogous (Py, 2-ClPy, and 2,6-Cl_2Py) were used as base additive (Table 1, entries 8, 7, and 4, respectively), dimerized product **2a** was isolated in moderate to good yield. Other base additives such as DMAP, triethylamine or DBU (Table 1, entries 9, 10 and 11, respectively) were found to be ineffective in this one-pot approach. 2-ClPy functioned as base additive was thereby screened for further investigation. By comparison, refluxing is necessary for reaction completeness (Table 1, entries 4, 5 and 6), whereas half hour is enough (Table 1, entries 2, 3 and 4). Dimerization may also occur using Tf_2O as the sole activating reagent but with relatively lower yield (Table 1, entries 1 and 2). The mechanism presented in Scheme 1 showed slightly difference between with or without the

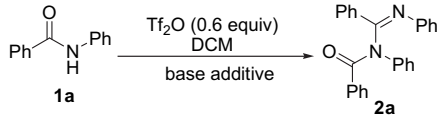
* Corresponding authors. Tel./fax: +86 571 87951512.
E-mail addresses: pinglu@zju.edu.cn (P. Lu), orgwyg@zju.edu.cn (Y. Wang).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.12.034



Scheme 1. Formation of amidine **2a**.

Table 1
Survey of reaction conditions for preparation of amidine **2a**



Entry	Base additive (equiv)	Temperature (°C)	Time (h)	Yield[a] (%)
1	none	−78 ~ reflux	8	50
2	2-ClPy (0.6)	−78 ~ reflux	8	88
3	2-ClPy (0.6)	−78 ~ reflux	3	86
4	2-ClPy (0.6)	−78 ~ reflux	0.5	85
5	2-ClPy (0.6)	−78 ~ rt.	0.5	75
6	2-ClPy (0.6)	−78	0.5	20
7	2,6-Cl_2Py (0.6)	−78 ~ reflux	0.5	78
8	Py (0.6)	−78 ~ reflux	0.5	80
9	DMAP (0.6)	−78 ~ reflux	0.5	trace
10	TEA (0.6)	−78 ~ reflux	0.5	trace
11	DBU (0.6)	−78 ~ reflux	0.5	trace

[a] Isolated yield refers to amide **1a**.

participation of 2-ClPy. In comparison with phosphoric anhydride[14] as activating reagent, our method is more general and efficient.

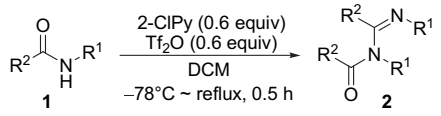
Using the optimized reaction condition, we explored the scope of the reaction with a variety of the accessible amides (Table 2). In all cases, amides **1** proceeded to furnish the corresponding substituted amidines **2**. Both the amides with an aromatic acyl (Table 2, entries 1–7) and the amides with an aliphatic acyl (Table 2, entry 8) gave good to excellent yields (79–90%). The amide with heterocycles such as furan or thiophene (Table 2, entries 9 and 10, respectively) could also undergo the reaction. Moreover, the inductive effects of the *N*-aryl side of amide on the reaction were insignificant (Table 2, entries 1, 3, 5 and 6).

When the amides **3a**–**3g**, derived from symmetric 1,2-diaminobenzenes, were used as the substrates, *N*-acyl benzimidazoles **4** were constructed in moderate yields (Table 3). Unsymmetrically substituted diamides **5** afforded a mixture of two isomers **6** and **7** (Table 4). The structure of **7c** was unambiguously determined by X-ray diffraction analysis.[15]

Since benzimidazoles are of wide applications as drugs with biological and pharmaceutical impact,[16] and as molecular precursors for the development of ligands,[17] dyes[18] and polymers,[19] our reaction provides a novel synthetic method leading to this important class of heterocyclic compounds.

Using optical diamide **8** as the substrate, derived from (1*R*,2*R*)-cyclohexane-1,2-diamine, chrial dihydroimidazoles **9** were obtained in excellent yields (Scheme 2).

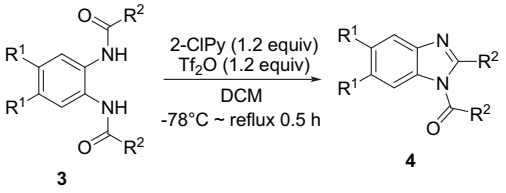
Table 2
Synthesis of amidines **2**[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	Ph	Ph	**2a**	85
2	Ph	2-ClC_6H_4	**2b**	85
3	4-$MeOC_6H_4$	Ph	**2c**	84
4	2-Me-4-MeO-C_6H_3	Ph	**2d**	80
5	4-MeC_6H_4	Ph	**2e**	79
6	4-BrC_6H_4	Ph	**2f**	83
7	2-MeC_6H_4	Ph	**2g**	90
8	Ph	*n*-C_5H_{11}	**2h**	89
9	Ph		**2i**	84
10	4-MeC_6H_4		**2j**	82

[a] All reactions were performed on 1 mmol of amide.
[b] Isolated yield refers to amide.

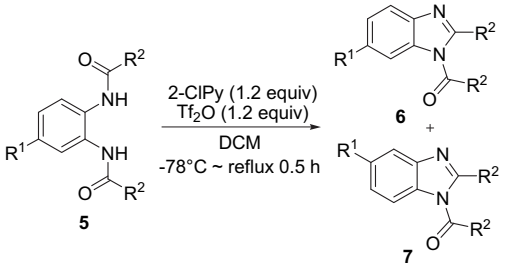
Table 3
Synthesis of 1-acyl-benzimidazoles **4**[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	H	Ph	**4a**	62
2	H	4-ClC_6H_4	**4b**	58
3	Cl	Ph	**4c**	60
4	Cl	4-MeC_6H_4	**4d**	66
5	CH_3	Ph	**4e**	55
6	CH_3	4-ClC_6H_4	**4f**	51
7	H	2-MeC_6H_4	**4g**	58

[a] All reactions were performed on 1 mmol of amide.
[b] Isolated yield refers to amide.

Table 4
Synthesis of 1-acyl-benzimidazoles **6** and **7**[a]



Entry	R^1	R^2	Product	Yield[c] (%)
1	Me	Ph	**6a**+**7a** (4:3)[b]	53
2	Cl	2-MeC_6H_4	**6b**	32
			7b	24
3	NO_2	Ph	**6c**	24
			7c	30

[a] All reactions were performed on 1 mmol of amide **5**.
[b] The ratio for **6a**/**7a** was determined by ^{1}H NMR spectra.
[c] Isolated yield refers to amide.