ORGANIC LETTERS

2010
Vol. 12, No. 17
3902−3905

Simple and Efficient Preparation of 2,5-Disubstituted Oxazoles via a Metal-Free-Catalyzed Cascade Cyclization

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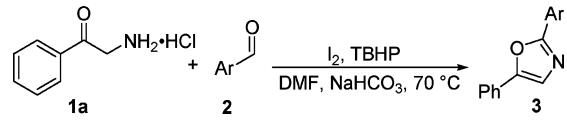
Received July 11, 2010

ABSTRACT



A practical and simple synthesis of 2,5-disubstituted oxazoles was developed via an iodine-catalyzed tandem oxidative cyclization. A wide range of common commercial aromatic aldehydes can be used as reaction substrates, which displayed excellent functional group compatibility in this reaction.

Oxazoles are an important class of heterocycles which widely exist in natural compounds, fluorescent dyes, and pharmaceuticals.[1] Many compounds containing an oxazole motif exhibit potent biological activities.[2] Moreover, they are also versatile synthetic blocks in organic synthesis.[3] Many strategies were reported for the synthesis of oxazole derivatives.[4] Traditionally, substituted oxazoles were accessed via ring derivatization or cyclization of acyclic precursors.[5] For example, some conventional methods for the preparation of oxazoles involved the cyclodehydration of α-acylaminoketones (Robinson−Gabriel reaction)[6] and the oxidation of oxazolines.[7]

Recently, direct functionalization of oxazole has been developed via transition-metal-catalyzed coupling reactions.[8] Although these methods provided convenient access to substituted oxazoles, there are some limitations associated with them, such as harsh reaction conditions and inaccessible synthetic precursors. Therefore, the development of more efficient and practical protocols still is highly desirable.

C−C bond and C−heteroatom bonds have been successfully constructed in the presence of a Lewis acid and an

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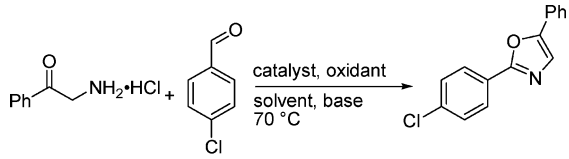
10.1021/ol101596s
Published on Web 08/03/2010

oxidant in recent years.[9] In continuation of our endeavors to use iodine and TBHP as a catalyst system to construct heterocycles,[10] herein, we report a simple and efficient iodine-catalyzed synthesis of 2,5-disubstituted oxazoles from easily available starting materials under mild conditions.

Our investigation began with the reaction of 2-amino-1-phenylethanone hydrochloride (**1a**) and 4-chlorobenzaldehyde (**2h**) in the presence of Lewis acid and TBHP[11] in DMF. The results were summarized in Table 1. First, the

Table 1. Optimization of Reaction Conditions[a]



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

entry	catalyst	oxidant	base	solvent	yield (%)[b]
1	$CuCl_2$	TBHP	$NaHCO_3$	DMF	0
2	$FeCl_3$	TBHP	$NaHCO_3$	DMF	0
3	I_2	TBHP	$NaHCO_3$	DMF	52
4	–	TBHP	$NaHCO_3$	DMF	0
5	I_2	H_2O_2	$NaHCO_3$	DMF	19
6	I_2	*m*-CPBA	$NaHCO_3$	DMF	32
7	I_2	*t*-BuOO*t*-Bu	$NaHCO_3$	DMF	41
8	I_2	–	$NaHCO_3$	DMF	23
9	I_2	TBHP	K_2CO_3	DMF	47
10	I_2	TBHP	Cs_2CO_3	DMF	43
11	I_2	TBHP	–	DMF	18
12	I_2	TBHP	$NaHCO_3$	C_2H_5OH	42
13	I_2	TBHP	$NaHCO_3$	THF	0
14	I_2	TBHP	$NaHCO_3$	DCE	39
15	I_2	TBHP	$NaHCO_3$	CH_3CN	46
16[c]	I_2	TBHP	$NaHCO_3$	DMF	65
17[d]	I_2	TBHP	$NaHCO_3$	DMF	79
18[e]	I_2	TBHP	$NaHCO_3$	DMF	0

[a] Reaction conditions: **1a** (1.5 equiv), **2h** (1.0 equiv, 0.2 mmol), base (1.0 equiv), catalyst (0.3 equiv), oxidant (1.5 equiv) in solvent (1 mL). [b] Isolated yield. [c] 3.0 equiv of **1a**. [d] 4.0 equiv of **1a**. [e] The reaction was carried out at room temperature for 10 h.

catalytic activities of different metal salts were examined as Lewis acids in this reaction; however, no catalytic activity was observed for this reaction (Table 1, entries 1−2). It was found that the reaction proceeded smoothly when iodine was employed as a catalyst (Table 1, entry 3). Without iodine the reaction did not work and no product was detected (Table 1, entry 4), which indicated that iodine was an essential catalyst for this reaction. Then we investigated the effect of different oxidants on the reaction. Different oxidants, such as *t*-BuOO*t*-Bu, H_2O_2, *m*-CPBA, were employed in this reaction respectively (Table 1, entries 5−7). The experimental results indicated that TBHP was the most effective for the reaction. When the reaction was carried out without an oxidant, the reaction afforded the desired product with a low yield of 23% (Table 1, entry 8), which suggested that the oxidant also played an important role in the reaction. Then we investigated the influence of base on the reaction and found that sodium hydrogen carbonate was the most effective for the reaction (Table 1, entries 9−11). Subsequently, the reaction solvent was optimized (Table 1, entries 12−15). When DMF was replaced with THF, no product was observed (Table 1, entry 13). When ethanol, DCE, or CH_3CN was employed as solvent respectively, low yields of the product were obtained. After optimization, DMF was the best solvent for this reaction. Finally, the dosage of **1a** was investigated. When the amount of **1a** was increased to 3.0 equiv from 1.5 equiv, the corresponding yield enhanced from 52% to 65%. While the loading of **1a** was continuously increased to 4.0 equiv, the yield enhanced further to 79% from 65% (Table 1, entries 16−17). When the reaction was performed at room temperature, no desired product was obtained (Table 1, entry 18). As a result, the optimal reaction conditions were established as follows: 4.0 equiv of **1a** and 1.0 equiv of **2h** as reaction substrates, 1.0 equiv of sodium hydrogen carbonate as a base, 0.3 equiv of iodine as a catalyst, 1.5 equiv of TBHP as an oxidant, and DMF as the solvent.

With the optimal conditions in hand, we then investigated the substitution effect of the aromatic ring of the aldehydes on the reaction in order to extend the scope of the reaction substrates. The results are summarized in Table 2 (entries 1−16). It was found that there was little difference between the substitution effect of an electron-donating group and that of an electron-withdrawing group, although it seemed as if electron-donating substituents favored this reaction more than the electron-withdrawing substituents. Similarly, the effect of steric hindrance had little influence on the reaction despite a slight tendency toward ortho-substitution. Moreover, these phenyl aldehyde substrates could be replaced with other aromatic aldehydes. When (*Z*)-3-phenylacrylaldehyde and 2-naphthaldehyde were chosen as the reactants, for example, the reactions also gave the corresponding products in 76% and 75% yields respectively (Table 2, entries 17−18). Heterocyclic aldehydes can also be the substrates, and the corresponding products can be obtained with moderate to good yields (Table 2, entries 19−21). When multisubstituted aldehydes were employed as the reactants, the reactions also proceeded smoothly to give the corresponding products with good yields (Table 2, entries 22−23). When a heterocycle was chosen as a substituent of the phenyl ring of aldehyde, the reaction also afforded the corresponding product in 82% yield (Table 2, entry 24).

In order to examine the practicability of this developed methodology, annuloline (**6**) was selected as a target molecule, which was isolated from the roots of ryegrass and

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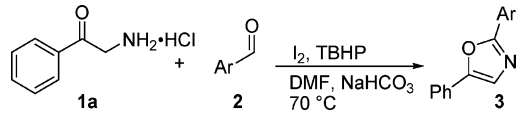
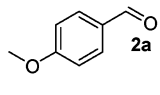
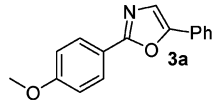
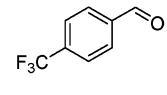
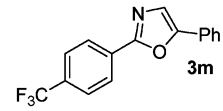
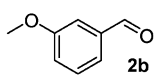
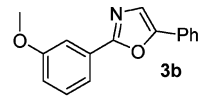
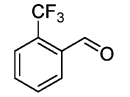
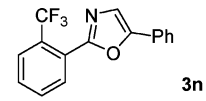
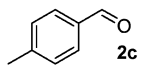
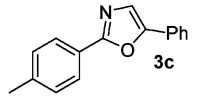
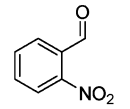
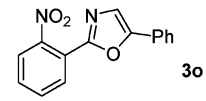
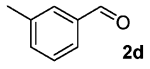
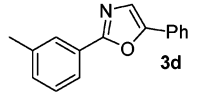
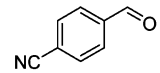
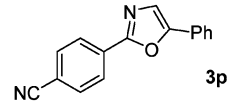
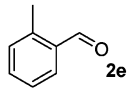
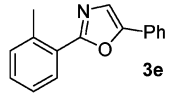
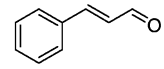
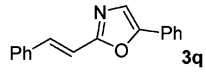
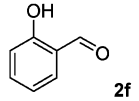
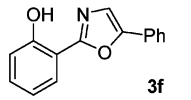
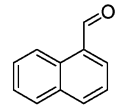
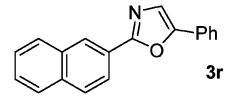
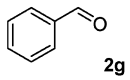
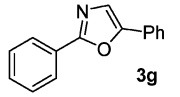
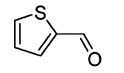
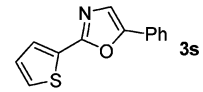
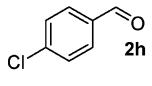
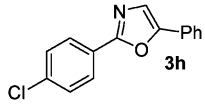
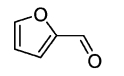
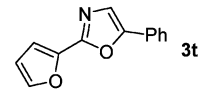
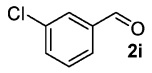
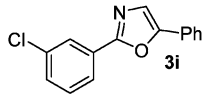
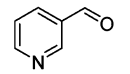
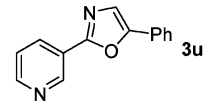
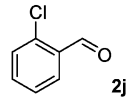
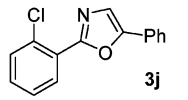
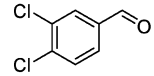
Table 2. Synthesis of 2,5-Disubstituted Oxazoles[a]



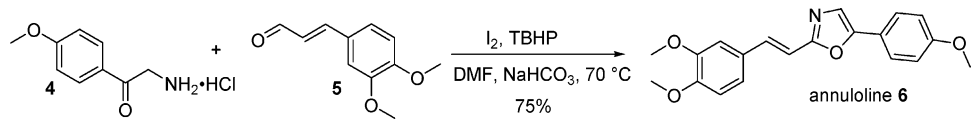
entry	substrate **2**	product **3**	yield (%)[b]	entry	substrate **2**	product **3**	yield (%)[b]
1	 **2a**	 **3a**	65	13	 **2m**	 **3m**	65
2	 **2b**	 **3b**	88	14	 **2n**	 **3n**	64
3	 **2c**	 **3c**	87	15	 **2o**	 **3o**	82
4	 **2d**	 **3d**	75	16	 **2p**	 **3p**	87
5	 **2e**	 **3e**	90	17	 **2q**	 **3q**	76
6	 **2f**	 **3f**	91	18	 **2r**	 **3r**	75
7	 **2g**	 **3g**	77	19	 **2s**	 **3s**	75
8	 **2h**	 **3h**	79	20	 **2t**	 **3t**	66
9	 **2i**	 **3i**	75	21	 **2u**	 **3u**	51
10	 **2j**	 **3j**	82	22	 **2v**	**3v**	85
11	**2k**	**3k**	81	23	**2w**	**3w**	81
12	**2l**	**3l**	76	24	**2x**	**3x**	82

[a] Reaction conditions: **1a** (0.8 mmol), **2** (1.0 equiv, 0.2 mmol), $NaHCO_3$ (0.2 mmol), iodine (0.06 mmol), TBHP (0.3 mmol) in DMF (1 mL). [b] Isolated yield.

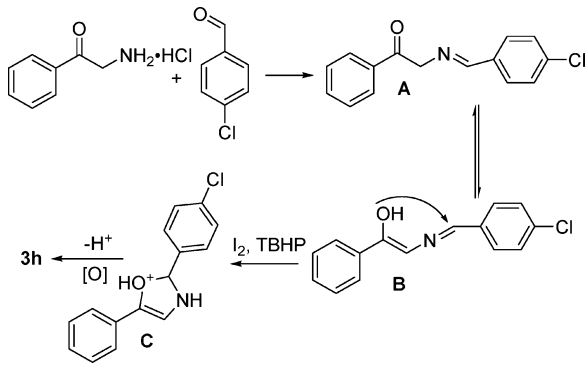
was the first isolated natural product containing an oxazole substructure. Previous reports on the preparation of annuloline generally involved the preparation of building blocks.[8a,12] By using this new method, the preparation of annuloline (**6**) was achieved by the reaction of **4** with **5** in one step, giving the target annuloline (**6**) with a yield of 75% (Scheme 1).

Moreover, a possible mechanism of the reaction was proposed as shown in Scheme 2 according to the results above. First, the reaction of **1a** with **2h** formed **A**, and then

Scheme 1. Synthesis of Annuloline



Scheme 2. Possible Pathway of the Reaction



B was obtained by the enolization of **A**. Then an intramolecular attack of the oxygen atom provided **C** in the presence of iodine and TBHP. Finally, **C** gave the product **3h** by deprotonation and oxidation.

(12) (a) Molina, P.; Fresneda, P. M.; Almendros, P. *Heterocycles* **1993**, *36*, 2255. (b) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliott, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657.

In summary, a practical and efficient synthesis of 2,5-disubstituted oxazoles was described via an iodine-catalyzed tandem process. The reaction gave the desired products from readily accessible substrates under mild conditions. The reaction did not involve any metal salt, excluding the residue of a metal ion in the products. Furthermore, the reaction showed a broad scope of substrates in which a wide range of common commercial aromatic aldehydes were employed, and these substrates displayed excellent functional group compatibility. Further application and limitation of this procedure are in progress in our laboratory.

Acknowledgment. We are grateful to the Natural Science Foundation of China (20932002, 20972144, 20628202, 20772188, and 90813008) and the Chinese Academy of Sciences for support.

Supporting Information Available: Typical procedure for the reaction and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101596S