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Metal-Free sp³ C–H Functionalization: PABS/I_2-Promoted Synthesis of Polysubstituted Oxazole Derivatives from Arylethanones and 2-Amino-2-alkyl/arylacetic Acid

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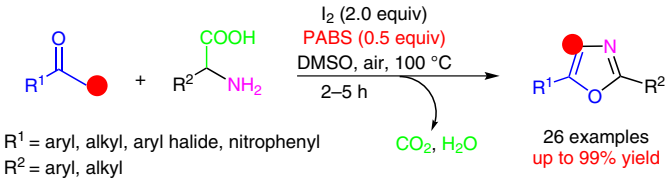

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Abstract A nonmetal-catalyzed process for the synthesis of polysubstituted oxazoles from inexpensive and readily available α-amino acids and methyl ketones is established. This reaction is proposed to achieve oxidative cleavage of C(sp³)–H bonds, followed by decarboxylation and annulation. The mild reaction conditions employed in both cases enable the tolerance of a wide range of functional groups as well as high reaction efficiency.

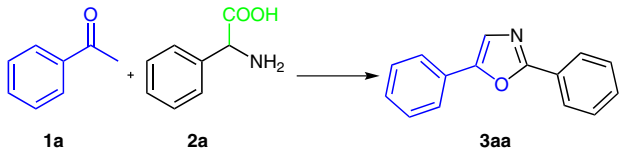
Key words nonmetal-catalyzed, oxazoles, sp³ C–H functionalization, high yield, amino acids

Oxazoles represent an important class of five-membered N-heterocyclic aromatic compounds.[1–3] They have attracted remarkable attention not only because they serve as one of the key building blocks in various natural products, pharmaceuticals, and synthetic intermediates, but also due to their biological activities such as bacteriostatic and fungistatic activities, fluorescent whitening activities, and scintillator properties.[4–19] In addition, oxazole derivatives are also employed as corrosion inhibitors[20,21] and in photography.[15] A wide variety of synthetic routes have been developed for oxazole derivatives.[22–29] Classical synthesis of oxazole derivatives includes the Robinson–Gabriel synthesis, the Fischer synthesis, and the Van Leusen reaction.[30] In 2010, an elegant work for the synthesis of polysubstituted oxazoles using copper salts were reported by Wang and coworkers.[23] And then, the excellent preparations of substituted oxazoles from benzylamines were consecutively reported.[24–27] More recently, amino acids as a sort of inexpensive, environmentally friendly, and highly atom-efficient starting materials have attracted the attention of many chemists. The exploitation of the cyclization reaction that enables the realization of transformation in good yields and mild-condition manner still remains challenging. We found a kind of additive (*p*-aminobenzenesulfonic acid) to greatly increase the efficiency of a similar reaction in the product. Herein, we report a facile synthesis of 2,5-disubstituted oxazoles from α-amino acids via PABS/I_2-promoted oxidative cyclization of ketone C(sp³)–N bonds (resulting in C–N bond formation). This nonmetal-catalyzed reaction with easily available starting material and high yields can potentially serve as a new practical route to the synthesis of oxazole derivatives.

Initial experiments were carried out using acetophenone (**1a**) and phenylglycine (**2a**) as model substrates. The mixture was stirred without any protection gas. A range of oxidants, such as I_2 (1.0 and 2.0 equiv), CuI (1.0 equiv), and NIS (1.0 equiv) were examined, and I_2 (2.0 equiv) showed the best capability to promote the reaction and gave the desired 2,5-diphenyloxazole in 66% yield (Table 1, entries 1–4). Unexpectedly, the yield decreased when using more than 2.5 equivalents of I_2 as oxidant (Table 1, entry 5). In the optimization of the reaction temperature, it was found that the reaction has the best yield at 100 °C (Table 1, entries 4, 6 and 7). After that, we examined three different solvents (Table 1, entries 8 and 9), interestingly, none of the other aprotic polar solvents afforded the product except DMSO. Since acid can promote the formation of intermediate **D**, including PivOH (1.0 equiv), TsOH (1.0 equiv), AcOH (1.0 equiv), and PABS (1.0 equiv), were tested to improve the yield. The reaction with PABS (0.5 equiv) produced 2,5-di-

phenyloxazole (**3a**) in high yield (90%, Table 1, entries 10–15). Gas atmosphere, such as O_2 and N_2, was also tested but neither gave better yields (Table 1, entries 16 and 17).

Table 1 Optimization of the Reaction Conditions[a]



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

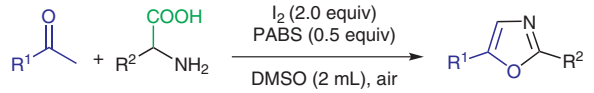
Entry	Oxidant (equiv)	Additive (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	I_2 (1.0)	–	DMSO	100	10
2	CuI (1.0)	–	DMSO	100	9
3	NIS (1.0)	–	DMSO	100	trace
4	I_2 (2.0)	–	DMSO	100	66
5	I_2 (2.5)	–	DMSO	100	63
6	I_2 (2.0)	–	DMSO	80	23
7	I_2 (2.0)	–	DMSO	120	58
8	I_2 (2.0)	–	DMF	100	trace
9	I_2 (2.0)	–	DMA	100	trace
10	I_2 (2.0)	PivOH (1.0)	DMSO	100	63
11	I_2 (2.0)	TsOH (1.0)	DMSO	100	76
12	I_2 (2.0)	AcOH (1.0)	DMSO	100	58
13[c]	I_2 (2.0)	PABS (1.0)	DMSO	100	89
14	**I_2 (2.0)**	**PABS (0.5)**	**DMSO**	**100**	**90**
15	I_2 (2.0)	PABS (0.3)	DMSO	100	56
16[d]	I_2 (2.0)	PABS (0.5)	DMSO	100	90
17[e]	I_2 (2.0)	PABS (0.5)	DMSO	100	85

[a] Reaction conditions: **1a** (0.32 mmol), **2a** (0.38 mmol), solvent (2 mL), 4 h.
[b] All yields are isolated products.
[c] PABS = *p*-aminobenzenesulfonic acid.
[d] The reaction was carried out under a O_2 atmosphere.
[e] The reaction was carried out under a N_2 atmosphere; DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, DMA = *N*,*N*-dimethylacetamide.

Using the molecular iodine/*p*-aminobenzenesulfonic acid oxidant system in DMSO (Table 1, entry 14), we examined the substrates scope of this oxidative cyclization for the synthesis of 2,5-diphenyloxazole, the results are shown in Table 2. Generally, acetophenone and its derivatives with either electron-withdrawing or electron-donating groups on the aromatic rings could readily participate in the reactions and result in high yields (**3ba**, 95%; **3ca**, 84%; **3ea**, 94%; **3fa**, 99%; **3la**, 85%; **3oa**, 90%; **3pa**, 88%). A halogen at the 2-, 3- or 4-position imparted mild reactivity furnishing the corresponding products in perfect yields (**3da**, 87%; **3ga**, 93%; **3ha**, 95%; **3ma**, 97%; **3na**, 98%) with decent recovery of the unreactive precursors. A favorable yield was observed in the case of 2-substituted phenyl (**3qa**, 89%), which indicated that steric hindrance did not affect the reaction efficiency. Likewise, 3,4-$(MeO)_2$ and 3,4-Cl_2 were suitable substrates for this process, which produced the corresponding compounds in excellent yields (**3ja**, 99%; **3ka**, 93%). Besides, variation of the R^1 substituent of **1** showed that 1-naphthyl and 2-naphthyl groups (**3ra**, 82%; **3sa**, 92%) can also be converted into the corresponding 2,5-diphenyloxazole through the same reaction conditions. Notably, the reaction with 4-methylpentan-2-one could also proceed to furnish the desired product **3ta** in 42% isolated yield, thus indicating that alkyl methyl ketone could produce the corresponding products.

This oxidative decarboxylative annulation was further expanded to a range of substituted α-amino acids **2** (Table 2). The introduction of alkyl groups [R^2 = *n*-Pr, *i*-Pr, and *i*-Bu] at

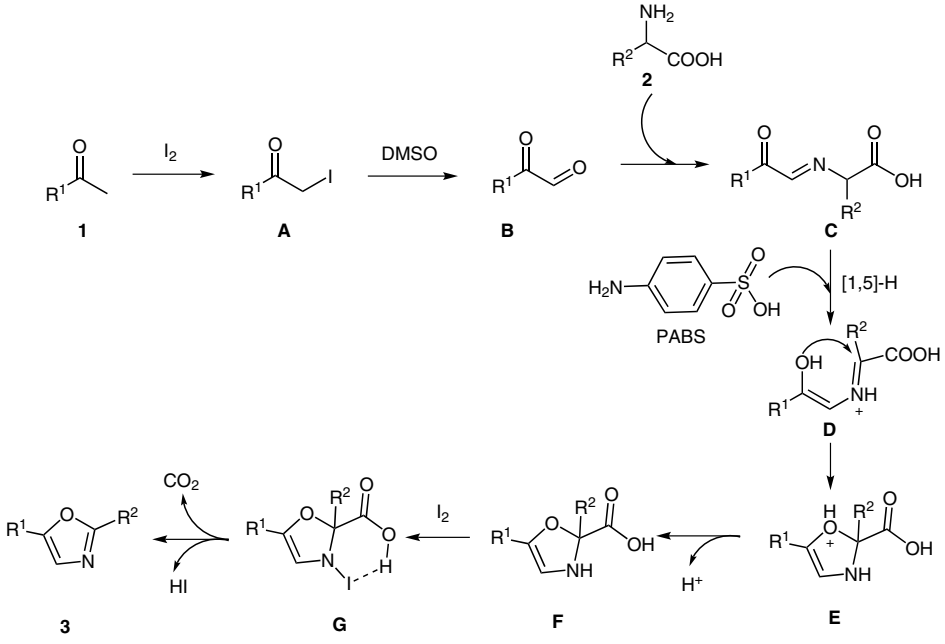
Table 2 Reaction Scope of Methyl Ketones and Amino Acid[a]



1 **2** **3**

Entry	R^1	R^2	Product	Yield (%)[b]
1	**1a** Ph	**2a** Ph	**3aa**	90
2	**1b** 2-MeC_6H_4	**2a** Ph	**3ba**	95
3	**1c** 2-$MeOC_6H_4$	**2a** Ph	**3ca**	84
4	**1d** 2-ClC_6H_4	**2a** Ph	**3da**	87
5	**1e** 3-MeC_6H_4	**2a** Ph	**3ea**	94
6	**1f** 3-$MeOC_6H_4$	**2a** Ph	**3fa**	99
7	**1g** 3-ClC_6H_4	**2a** Ph	**3ga**	93
8	**1h** 3-BrC_6H_4	**2a** Ph	**3ha**	95
9	**1i** 3-$O_2NC_6H_4$	**2a** Ph	**3ia**	91
10	**1j** 3,4-$(MeO)_2C_6H_3$	**2a** Ph	**3ja**	99
11	**1k** 3,4-$Cl_2C_6H_3$	**2a** Ph	**3ka**	93
12	**1l** 4-$MeOC_6H_4$	**2a** Ph	**3la**	85
13	**1m** 4-FC_6H_4	**2a** Ph	**3ma**	97
14	**1n** 4-ClC_6H_4	**2a** Ph	**3na**	98
15	**1o** 4-$O_2NC_6H_4$	**2a** Ph	**3oa**	90
16	**1p** 4-$F_3CC_6H_4$	**2a** Ph	**3pa**	88
17	**1q** 4-PhC_6H_4	**2a** Ph	**3qa**	89
18	**1r** 1-naphthyl	**2a** Ph	**3ra**	82
19	**1s** 2-naphthyl	**2a** Ph	**3sa**	92
20	**1t** $Me_2C_2H_3$	**2a** Ph	**3ta**	42
21	**1a** Ph	**2b** *n*-Pr	**3ab**	75
22	**1a** Ph	**2c** *i*-Pr	**3ac**	70
23	**1a** Ph	**2d** MeCH(OH)	**3ad**	39
24	**1a** Ph	**2e** $MeSCH_2CH_2$	**3ae**	58
25	**1a** Ph	**2f** *i*-Bu	**3af**	82
26	**1a** Ph	**2g** Bn	**3ag**	48

[a] Reaction conditions: **1** (0.32 mmol), **2** (0.38 mmol), I_2 (2.0 equiv), PABS (0.5 equiv), DMSO (2 mL), at 100 °C, under air 2–5 h.
[b] All yields are isolated products.



Scheme 1

the α-amino acids were well tolerated in the reaction (**3ab**, 75%; **3ac**, 70%; **3af**, 82%). Meanwhile, it was noteworthy that an unprotected hydroxyl group could also undergo this process, although in lower yield (**3ad**, 39%). Additionally, yields of oxazoles **3ae** (58%) and **3ag** (48%) with $MeSCH_2CH_2$ and benzyl substituents were distinctly lower even under different reaction conditions, which appear to be sensitive to the transformation time.

On the basis of the previous reports,[23–29] a plausible mechanism was proposed in Scheme 1. It may undergo according to the following procedures. Initially, the substrates **1** were converted into the intermediate α-iodo acetophenone **A** in the presence of I_2. Subsequently, **A** was oxidized by DMSO to **B**. Then, amino acids **2** reacted with **B** to afford **C**, **C** isomerized to **D** via a [1,5]-H shift. *p*-Aminobenzenesulfonic acid (PABS) acts as acid that promoted the reaction by increasing the electrophilicity of C-1 on **D** through coordination with nitrogen, providing a good electrophilic section for the nucleophilic hydroxyl group, which underwent an intramolecular cyclization furnishing the intermediate **E**. Consequently, **E** converted into **F** through deprotonation, and an iodine-mediated oxidative decarboxylation of **G** generated the desired product **3** through the release of CO_2 and HI.

In conclusion, we have developed a new strategy for the synthesis of 2,5-diphenyloxazole derivatives via the non-metal-catalyzed C–H activation. Besides, the amenability of a wide variety of functional groups, the superiority of using readily available initial substrates greatly boosts the reaction's utility of this protocol. Furthermore, the transformation proceeds with perfect yields to a variety of functional groups.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560660.

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(30) **Typical Procedure for the Preparation of 2,5-Diphenyloxazole**

A test tube was charged with **1a** (0.32 mmol), **2a** (0.38 mmol), I_2 (2.0 equiv), and PABS (0.5 equiv). Then DMSO (2 mL) was added to the reaction system. The reaction was stirred at 100 °C for 5 h. After cooling to r.t., the solvent diluted with EtOAc (10 mL) and washed with brine (5 mL) and dried over anhydrous Na_2SO_4. After the solvent was evaporated in vacuo, the residues were purified by column chromatography, eluting with PE–EtOAc to afford pure **3aa** as a yellow solid (64 mg, 90%); mp 58–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.08 (m, 2 H), 7.70–7.68 (m, 2 H), 7.48–7.39 (m, 6 H), 7.30 (t, *J* = 7.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.02, 151.14, 130.20, 128.81, 128.70, 128.31, 127.91, 127.37, 126.18, 124.08, 123.37. ESI-HRMS: *m/z* calcd for $C_{15}H_{12}NO$ [M + H]$^+$: 222.0914; found: 222.0916.