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Title: Synthesis of 2-Amino Substituted Oxazoles from α-Amino Ketones and Isothiocyanates via Sequential Addition and I2-Mediated Desulfurative Cyclization

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COMMUNICATION

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Synthesis of 2-Amino Substituted Oxazoles from α-Amino Ketones and Isothiocyanates *via* Sequential Addition and I_2-Mediated Desulfurative Cyclization

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Abstract. Oxazol-2-amines were synthesized by annulation of α-amino ketones and isothiocyanates. This sequential synthetic process involves addition of α-amino ketones to isothiocyanates and I_2-promoted desulfurative cyclization omitting isolation of the less stable thiourea intermediates. It is transition metal-free and operationally simple, providing access to a variety of 2-amino substituted oxazole derivatives under mild reaction conditions.

Keywords: oxazol-2-amine; iodine; desulfurative cyclization; α-amino ketone; isothiocyanate

Oxazol-2-amine is a privileged structure motif found in inhibitors of inosine monophosphate dehydrogenase (IMPDH)[1] and other molecules with enzyme inhibitory,[2] antiviral,[3] analgesic,[4] and antitubercular[5] activities. Nevertheless, among numerous methods for oxazole synthesis, only a few pathways provide access to oxazole derivatives bearing an amine substituent.[6] The synthesis of oxazol-2-amines in drug discovery has relied on the PPh_3-mediated annulations of *β*-ketoazides and isothiocyanates.[1-4, 7] In this reaction, two substrates form a carbodiimide which then undergoes intramolecular cycloaddition to give an oxazol-2-amine product. In 2015, Rassadin and Kukushkin[8] described a gold-catalyzed cyclization of terminal alkynes and cyanamides forming substituted 2-aminooxazoles and subsequently, Soeta and Ukaji[9] developed a one-pot reaction for the synthesis of oxazol-2-amines using isocyanide dichlorides. Recently, Dubovtsev and Kukushkin[10] synthesized 2-amino-1,3-oxazoles via a three-component [2+2+1] gold(I)-catalyzed reaction of internal alkynes, cyanamides, and 2-chloropyridine *N*-oxide. Moreover, several synthetic approaches leading to 4-amino or 5-amino substituted oxazoles have been reported by annulation reactions of ynamides and corresponding building blocks in the presence of gold, cobalt or selenium catalysts.[11]

Desulfurative cyclization of readily accessible thiourea or thiosemicarbazide intermediates has become a valuable method for the construction of various amine-substituted heterocyclic skeletons, such as (fused) 1,2,4-triazole,[12] benzimidazole,[13] benzothiazole/benzoxazole,[14] and 1,3,4-oxadiazole/thiadiazole.[15] However, to the best of our knowledge, reactions for the synthesis of oxazol-2-amines *via* this cyclodesulfurization strategy have not been investigated to date. Herein, we describe an annulation reaction of α-amino ketones and isothiocyanates in the presence of molecular iodine[16] leading to 2-amino substituted oxazole derivatives.

Initially, we used 2-aminoacetophenone hydrochloride (**1a**) as a model substrate for the optimization of reaction conditions leading to oxazol-2-amine (**4a**) (Table 1). The addition of **1a** to phenyl isothiocyanate (**2a**) under basic conditions formed a thiourea intermediate (**3a**). In view of the poor stability of **3a**, the above mixture was promptly treated with iodine upon the completion of the first step addition. Solvent screening (entries 1−8) demonstrated that this transformation proceeds well in MeCN and afforded the expected product (**4a**) in 82% yield (entry 5). The structure of oxazol-2-amine **4a** was confirmed by X-ray crystallography.[17] Screening of inorganic and organic bases (entries 5, 9−15) indicated that K_2CO_3 is optimal (entry 5), and further optimization of the reaction conditions suggested that 60 °C is the ideal temperature for this transformation. The conversion was slow at lower temperatures (entries 16−17 vs entry 5) and the yield of the product was decreased at higher temperatures (entry 18 vs entry 5). Complete consumption of isothiocyanate **2a** requires at least 1.2 equiv. of the

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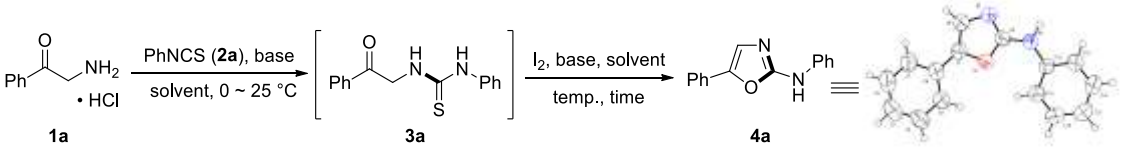
Table 1. Optimization of Reaction Conditions for the Synthesis of Oxazol-2-amine **4a**[a]



entry	**1a** (equiv)	I_2 (equiv)	base	solvent	temp.	time (h)[b]	yield (%)[c]
1	1.2	1.2	K_2CO_3	toluene	60 °C	1	13
2	1.2	1.2	K_2CO_3	DCE	60 °C	1	trace
3	1.2	1.2	K_2CO_3	THF	60 °C	1	16
4[d]	1.2	1.2	K_2CO_3	1,4-dioxane	60 °C	2	27
5	**1.2**	**1.2**	**K_2CO_3**	**MeCN**	**60 °C**	**1**	**82**
6[d]	1.2	1.2	K_2CO_3	DMSO	25 °C	1	54
7	1.2	1.2	K_2CO_3	DMF	60 °C	0.5	48
8	1.2	1.2	K_2CO_3	MeOH	60 °C	1	31
9	1.2	1.2	$NaHCO_3$	MeCN	60 °C	1	0
10	1.2	1.2	Na_2CO_3	MeCN	60 °C	1	30
11	1.2	1.2	Na_2HPO_4	MeCN	60 °C	1	0
12	1.2	1.2	NaOH	MeCN	60 °C	1	19
13	1.2	1.2	NaOAc	MeCN	60 °C	1	trace
14	1.2	1.2	Et_3N	MeCN	60 °C	1	55
15	1.2	1.2	DBU	MeCN	60 °C	2	trace
16	1.2	1.2	K_2CO_3	MeCN	25 °C	12	76
17	1.2	1.2	K_2CO_3	MeCN	40 °C	6	77
18	1.2	1.2	K_2CO_3	MeCN	82 °C	0.5	42
19	1.0	1.2	K_2CO_3	MeCN	60 °C	1	67
20	1.4	1.2	K_2CO_3	MeCN	60 °C	1	82
21	1.2	1.0	K_2CO_3	MeCN	60 °C	2	79
22	1.2	1.4	K_2CO_3	MeCN	60 °C	1	76
23[e]	1.2	1.2	K_2CO_3	MeCN	60 °C	1	66

[a] Optimal reaction conditions (entry 5): **1a** (0.6 mmol), **2a** (0.5 mmol), K_2CO_3 (1.1 mmol), MeCN (5 mL), 0 ~ 25 °C; then I_2 (0.6 mmol), K_2CO_3 (0.75 mmol), 60 °C. [b] The reaction time for the second step. [c] Isolated yields. [d] The first step at room temperature (25 °C). [e] In a one-pot manner with I_2 (0.6 mmol) added at the same time as K_2CO_3 (1.85 mmol).

substrate **1a** (entry 5 vs entries 19−20). The optimum amount of iodine is 1.2 equiv. (entry 5) and the yield was slightly affected by the addition of different quantities of iodine (entries 21−22). In addition, when iodine was added at the same time as K_2CO_3, this reaction also worked, but formed the product in decreased yield (entry 23). Thus, under the optimal reaction conditions, the iodine and the second portion of base was added upon the completion of the first step addition (entry 5).

To investigate the substrate scope, a variety of aryl isothiocyanates were subjected to the optimized reaction conditions (Table 1, entry 5). As shown in Scheme 1, the reaction of these isothiocyanate substrates (**2**) with 2-aminoacetophenone hydrochloride (**1a**) successfully produced the expected oxazol-2-amines in good to excellent yields. This synthetic process is compatible with both electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) on the aromatic ring (R^2) of the substrate **2**. The formation of the products was favored by the presence of EWGs at the *para*- (**4d**−**4i** *vs* **4b**−**4c**) and *ortho*- (**4m**−**4n** *vs* **4l**) positions, which may stabilize the carbodiimide intermediates (*cf.* Scheme 2). However, in the reaction of an alkyl isothiocyanate, no expected oxazol-2-amine product (**4o**) was formed, due probably to the poor stability of the corresponding carbodiimide intermediate.

We further examined the substrate scope of α-amino ketones. Under the optimal annulation conditions, the substituted α-amino ketone hydrochlorides (**1**) were also successfully converted to the oxazol-2-amine products (**4p**−**4w**) by the addition to the corresponding isothiocyanates

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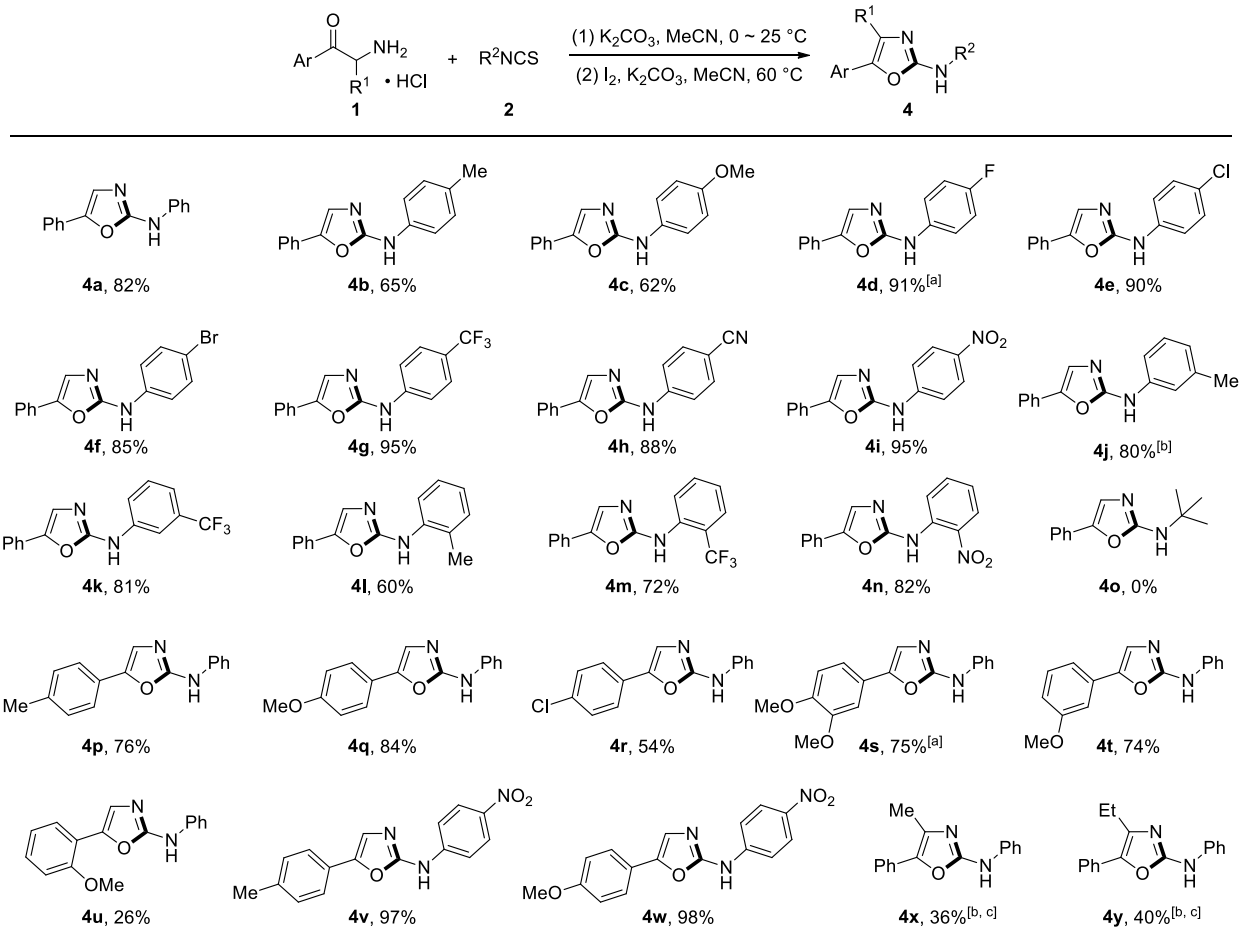
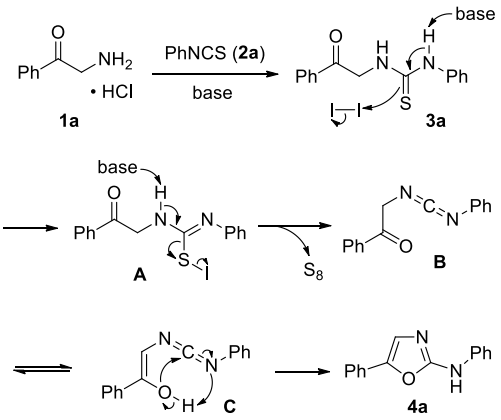


Scheme 1. Substrate Scope. Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), K_2CO_3 (1.1 mmol), MeCN (5 mL), 0 ~ 25 °C; then I_2 (0.6 mmol), K_2CO_3 (0.75 mmol), 60 °C (isolated yields are given). [a] The first step at 25 °C. [b] Both steps at 25 °C. [c] DMSO as the solvent.

followed by I_2-mediated desulfurative cyclization. The decreased yield of product **4r** (*vs* **4p**−**q**) could be due to the lower reactivity of the enol oxygen (*cf.* Scheme 2) caused by the presence of the electron-withdrawing chloro group. Annulations of α-amino ketones bearing EDGs and aryl isothiocyanates with EWGs porduced oxazol-2-amines in excellent yields (**4v**−**w**). The reactions of phenyl isothiocyanate with substrates in which R^1 is an alkyl group proceeded better in DMSO at room temperature (25 °C), affording the desired products (**4x**−**4y**) in moderate yields.

On the basis of the above results and the previous work,[7a] a tentative reaction mechanism is proposed and is shown in Scheme 2. Taking the formation of the product **4a** as an example, addition of 2-aminoacetophenone (**1a**) to the phenyl isothiocyanate (**2a**) in the presence of a base gives the thiourea intermediate (**3a**). Then, the base-promoted desulfurization[18] of compound **3a** by molecular iodine generates a carbodiimide intermediate[19] (**B**), which may revert to the tautomeric enol form (**C**). Subsequently, nucleophilic addition of the enol oxygen to the carbodiimide group and proton transfer leads to the oxazol-2-amine framework (**4a**).



Scheme 2. Proposed Mechanism

In summary, we have established a novel method for the synthesis of 2-amino substituted oxazoles from readily accessible substrates. Under mild reaction conditions, base-promoted addition of α-amino ketones to isothiocyanates generates thiourea intermediates, which then undergo desulfurative cyclization in the presence of iodine to afford the oxazol-2-amine products. This transition metal-free

protocol is operationally simple and broadly applicable to a range of α-amino ketone and isothiocyanate substrates.

Experimental Section

General Procedure for the Synthesis of the Products 4. To a mixture of 2-aminoacetophenone hydrochloride (**1**, 0.6 mmol) and the corresponding isothiocyanate (**2**, 0.5 mmol) in MeCN (5 mL) was added K_2CO_3 (152 mg, 1.1 mmol). After stirred at 0 °C for 1 h, the reaction was allowed to warm up to room temperature (25 °C) until TLC indicated the complete consumption of **2**. Then the reaction mixture was treated with K_2CO_3 (104 mg, 0.75 mmol) and iodine (152 mg, 0.6 mmol) in sequence, and maintained at 60 °C until TLC indicated the disappearance of the addition intermediate. Upon the completion of the reaction, it was quenched with 5% $Na_2S_2O_3$ (5 mL), diluted with brine (10 mL) and then extracted with EtOAc (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and then purified through silica gel column chromatography to afford the oxazol-2-amine product **4**.

Acknowledgements

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[17] CCDC 1977758 (**4a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[18] When the reaction was quenched with brine instead of 5% $Na_2S_2O_3$ and extracted with EtOAc, the resulting S_8 could be detected in the organic layer by TLC (R_f = 0.83, eluent: 100% petroleum ether).

[19] Carbodiimide intermediate **B** (or **C**) can be observed by TLC, but cannot be isolated due to the poor stability. For the synthesis and isolation of stable diaryl carbodiimides *via* similar desulfurization, see: a) A. R. Ali, H. Ghosh, B. K. Patel, *Tetrahedron Lett.* **2010**, *51*, 1019-1021; b) C. Duangkamol, M. Pattarawarapan, W. Phakhodee, *Monatsh. Chem.* **2016**, *147*, 1945-1949; c) D. A. Siriwardane, O. Kulikov, J. F. Reuther, B. M. Novak, *Macromolecules* **2017**, *50*, 832-840; d) C. Zhu, D. Xu, Y. Wei, *Synthesis* **2011**, 711-714.

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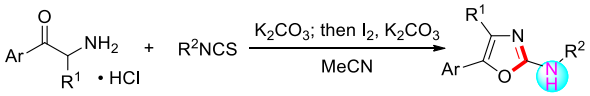

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