Iodine(III)-Promoted Synthesis of Oxazoles through Oxidative Cyclization of *N*-Styrylbenzamides

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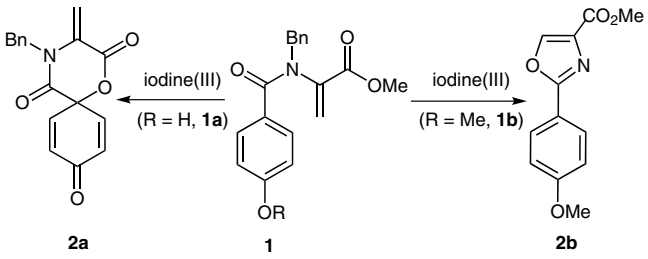
Abstract: The hypervalent iodine reagent $PhI(OTf)_2$, generated in situ, has been successfully utilized in an intramolecular oxidative cyclization of *N*-styrylbenzamides. In remarkably short reaction times, the desired 2,5-disubstituted oxazoles were isolated in high yields in this metal-free oxidative C–O bond-forming reaction.

Key words: hypervalent iodine, umpolung, oxazoles, cyclization, heterocycles

Hypervalent iodine(III) compounds (aryl-λ^3-iodanes) are readily available, nontoxic and environmentally benign reagents that have attracted a lot of interest in organic synthesis over the last decades due to their wide range of applications in oxidative coupling reactions.[1] In particular, oxidative C–C and C–X bond-forming reactions that contain oxidative phenol dearomatizations have found extensive applications in natural product synthesis.[2] Using this approach as a key step in a novel synthesis of arogenate (pretyrosine),[3] our group could recently show that 2-(4-hydroxybenzamido)acrylate (**1a**) undergoes iodine(III)-mediated oxidative spirolactonization to form δ-spirolactone **2a** (Scheme 1).[4] Interestingly, when the corresponding 2-(4-methoxybenzamido)acrylate (**1b**) was used as substrate, the formation of oxazole **2b** could be observed in low yields under slightly modified reaction conditions.



Scheme 1 Diversity in the iodine(III)-mediated reaction of benzamidoacrylates

As iodine(III) reagents have become more attractive in the oxidative transformation of olefins, we wondered whether this remarkable reactivity could be generalized towards an oxidative cyclization of only moderately functionalized enamides, such as easily accessible *N*-styrylbenzamides,[5] giving fast access to 2,5-diaryl oxazoles.[6] Such a reaction would be of great interest because oxazoles are an important class of heterocyclic compounds that are present in many biologically active natural products and pharmaceuticals.[7] So far, a variety of synthetic methods could be developed for the de novo synthesis of the oxazole motif.[8] Here, the intramolecular annulation of diverse functionalized enamides is a widely used approach because it offers simple and direct access to polysubstituted oxazoles from readily available starting materials.[9,10]

In particular, copper salts have been used as catalysts in this context, as reported independently by Buchwald and Stahl for the oxidative cyclization of enamides through vinylic C–H functionalization.[10] An iodobenzenediacetate (PIDA) mediated synthesis of oxazolylmethyl acetates was developed by Hanzawa and co-workers that is based on oxidative cycloisomerization of propargylamides.[11] Recently, Zhao and co-workers reported an intramolecular cyclization of amidoacrylates by utilizing a combination of PIDA and $BF_3{\cdot}OEt_2$, yielding 2,4,5-trisubstituted oxazoles.[12] Very recently, a similar strategy was applied by Harned and co-workers who reported the transformation of *N*-allyl amides into oxazolines.[13] However, *N*-styrylbenzamides, which give direct access to 2,5-diaryl oxazoles, have not yet been described in iodane-mediated cyclization reactions; their oxidative cyclization is systematically described in this article.

For our initial optimization studies we chose *N*-styrylbenzamide (**3a**) as substrate (Table 1). In initial experiments using the hypervalent iodine reagents PIDA and PIFA [bis(trifluoroacetoxy)iodobenzene] alone, only trace amounts of the desired oxazole product **4a** could be observed. Recently, Wirth and co-workers could show that the hypervalent iodine compound $PhI(OTf)_2$, which can be generated in situ from PIDA and TMSOTf,[14] is a highly reactive reagent in iodane-mediated oxyaminations.[6o] Therefore, we decided to also test the reactivity of $PhI(OTf)_2$ in our oxidative cyclization. We were pleased to observe that when PIDA was combined with TMSOTf in dichloromethane, **4a** could be isolated in a promising yield of 48% (Table 1, entry 1). Changing the solvent to Et_2O resulted in a slightly increased yield, which could be further improved by using a twofold excess of oxidant and additive (entries 2 and 3). The use of a mixture of CH_2Cl_2 and Et_2O, either in a 1:2 or 2:1 ratio, was also beneficial (entries 4 and 5). However, the best yield was obtained by using a 1:1 mixture of both solvents (entry 6). Applying a twofold excess of the additive gave no further improvement (entry 7), whereas using two equivalents of oxidant

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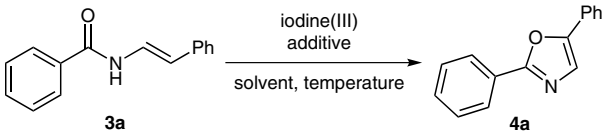
Table 1 Optimization Studies[a]



3a **4a**

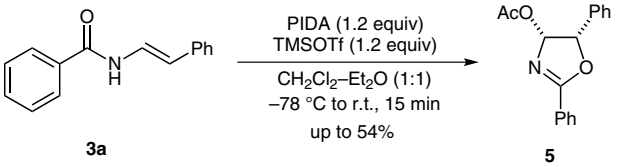
Entry	Iodine(III) (equiv)	Solvent	Additive (equiv)	Temp. (°C)	Time (h)	Yield (%)[b]
1	PIDA	CH_2Cl_2	TMSOTf	–78 to r.t.	24	48
2	PIDA	Et_2O	TMSOTf	–78 to r.t.	20	51
3	PIDA (2.0)	Et_2O	TMSOTf (2.0)	–78 to r.t.	16.5	55
4	PIDA	CH_2Cl_2–Et_2O (1:2)	TMSOTf	–78 to r.t.	16.5	57
5	PIDA	CH_2Cl_2–Et_2O (2:1)	TMSOTf	–78 to r.t.	22	58
6	PIDA	CH_2Cl_2–Et_2O (1:1)	TMSOTf	–78 to r.t.	20	72
7	PIDA	CH_2Cl_2–Et_2O (1:1)	TMSOTf (2.0)	–78 to r.t.	20	68
8	PIDA (2.0)	CH_2Cl_2–Et_2O (1:1)	TMSOTf (2.0)	–78 to r.t.	20	65
9	PIDA	CH_2Cl_2–Et_2O (1:1)	TMSOTf	–78 to r.t.	5.5	44
10	PIFA	CH_2Cl_2–Et_2O (1:1)	TMSOTf	–78 to r.t.	0.15	62
11	PIFA	CH_2Cl_2–Et_2O (1:1)	TMSOTf	–78 to 0	0.25	67
12	**PIFA**	**CH_2Cl_2–Et_2O (1:1)**	**TMSOTf (2.2)**	**–78 to 0**	**0.25**	**75**
13	PIDA	DCE	$BF_3{\cdot}OEt_2$	reflux	1	30

[a] Reaction conditions: **3a** (0.15 mmol), oxidant (1.2 equiv), additive (1.2 equiv), solvent (3 mL).
[b] Isolated yield after column chromatography.

and additive lowered the yield (entry 8). Although reaction monitoring showed full conversion of the starting material, the yield was diminished when the reaction time was decreased (see below; entry 9). When PIFA was used as the oxidant, yields dropped further but the reaction time could be decreased significantly from 20 hours to 15 minutes (entry 10). When the reaction was performed at 0 °C a significantly higher yield of **4a** was observed (67%, entry 11). Finally, using 2.2 equiv TMSOTf gave an optimized yield of 75% (entry 12). The combination of PIDA and $BF_3{\cdot}OEt_2$ in dichloroethane (DCE) at reflux, as described by Zhao and co-workers,[12] afforded only a poor yield of **4a** (entry 13). This result clearly indicates that the mild and selective reaction conditions that we have developed are complementary to other oxidative enamide cyclization reactions. With these optimized conditions in hand, we investigated the influence of the aryl group R^1 in the oxidative cyclization (Table 2).

Both, electron-rich as well as electron-poor aromatic substituents in the substrate were tolerated under the reaction conditions, giving the desired 2,5-diaryl oxazoles in up to 77% yield (Table 2, entries 1, 2, 4, 6, and 7). Only substrates bearing a substituent in the 3-position gave lower yields (entries 3, 5 and 8). However, a 3-nitro substituent seemed to have no negative influence on the outcome of the reaction (entry 9). CF_3-substituted substrates were also tolerated, giving **4k** and **4l** in 77 and 54% yield, respectively (entries 10 and 11). Cyclization of *N*-styryl nicotinamide gave **4m** in only low yields of 27% (entry 12). Furthermore, it is worth mentioning that the conformation of the enamide double bond had no influence on the outcome of this transformation since the reaction of (*Z*)-**3a** gave **4a** in comparable yields (72%).

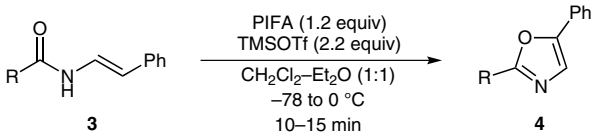
Finally, we further investigated the underlying reaction mechanism. As shown in the optimization studies, when using PIDA as the oxidant, high yields of the oxazole product were observed only after long reaction times. Extensive reaction monitoring by TLC revealed that the starting material **3a** was consumed within minutes upon stirring at room temperature. However, only trace amounts of the oxazole product could be detected at this point, whereas a byproduct with an R_f value similar to that of the starting material seemed to evolve in the reaction mixture. After stirring overnight, the initially formed byproduct disappeared and only the desired oxazole could be observed. When the reaction was stopped within minutes



3a **5**

Scheme 2 Formation of oxazoline

Table 2 Reaction Scope[a]

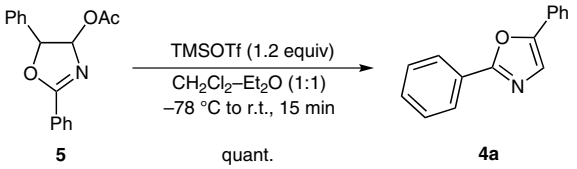


Entry	R	Oxazole	Yield (%)[b]
1	4-MeC_6H_4	**4b**	68
2	2-$EtOC_6H_4$	**4c**	70
3	3-$MeOC_6H_4$	**4d**	65
4	4-$MeOC_6H_4$	**4e**	77
5	3-FC_6H_4	**4f**	59
6	4-FC_6H_4	**4g**	77
7	2-ClC_6H_4	**4h**	72
8	3-ClC_6H_4	**4i**	55
9	3-$O_2NC_6H_4$	**4j**	72
10	4-$F_3CC_6H_4$	**4k**	77
11	3,5-$(CF_3)_2C_6H_3$	**4l**	54
12[c]	3-pyridyl	**4m**	27

[a] Reaction conditions: **3** (0.15 mmol), solvent (3 mL).
[b] Isolated yield after column chromatography.
[c] Reaction time 2.5 h.

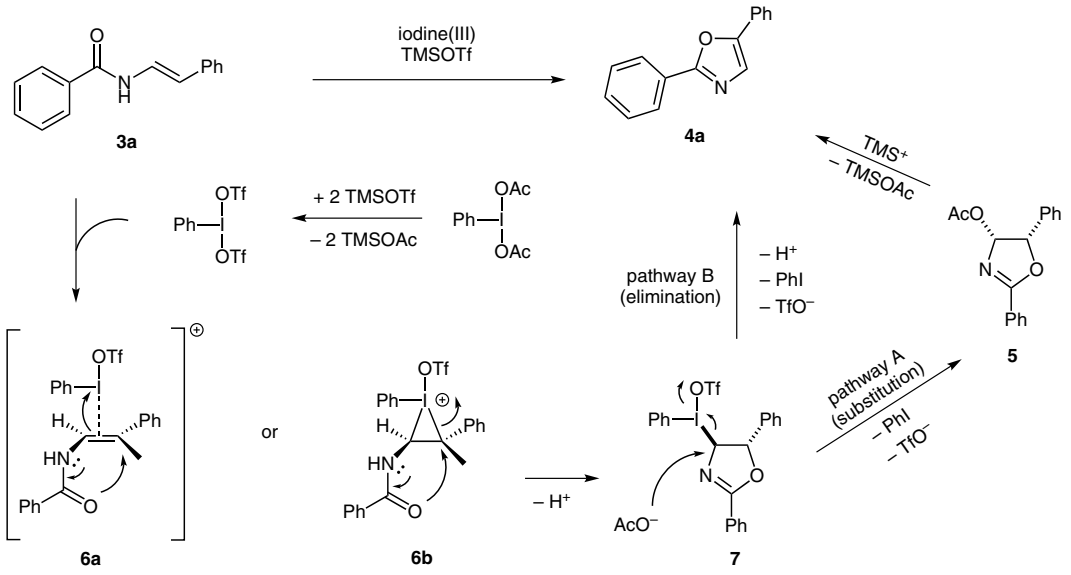
after stirring at room temperature, oxazoline acetate **5** could be isolated as a single diastereoisomer (*cis*) and this proved to be the byproduct initially formed in the reaction (Scheme 2). According to these results, we propose a mechanism for the oxidative cyclization as shown in Scheme 3. $PhI(OTf)_2$ generated in situ interacts with the alkene moiety of the enamide to form either activated olefin complex **6a** or iodonium ion **6b**, then 5-*endo* nucleophilic attack by the amide oxygen forms alkyl iodane **7**. The ability of the iodine(III) nucleus to act as a supernucleofuge makes further nucleophilic attack by acetate favorable, leading to the oxazoline **5** (pathway A).[15] In the final step, HOAc is eliminated to form **4a**. In a competing pathway, the oxazole is generated directly from alkyl iodane **7** through elimination, liberating iodobenzene and triflate (pathway B).

To verify that oxazoline **5** is truly an intermediate in the formation of the oxazole, attempts were made to convert **5** into **4a** under reaction conditions mimicking those of the oxidative cyclization. No reaction of **5** was observed in the presence of either NaOAc or NaOAc/TMSOTf. However, using solely TMSOTf, oxazoline **5** was completely consumed and oxazole **4a** could be isolated in quantitative yield (Scheme 4). These results suggest a Lewis acid promoted (i.e., TMS^+) abstraction of acetate in the formation of oxazole **4a** rather than elimination involving acetate acting as base. Further evidence for this conclusion is the enhanced reactivity observed for PIFA in the cyclization reaction. Because trifluoroacetate is a much worse nucleophile than acetate, pathway A can be neglected and direct elimination seems to be more favorable.



Scheme 4 Lewis acid promoted conversion of oxazoline

In conclusion, we have developed an efficient iodine(III)-mediated synthesis of 2,5-disubstituted oxazoles by an oxidative cyclization of *N*-styrylbenzamides.[16] By applying mild reaction conditions, a variety of oxazoles bearing electron-poor or electron-rich aromatic substituents in the



Scheme 3 Proposed reaction mechanism

5-position were obtained in good to high yields in remarkably short reaction time.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) **Synthesis of Oxazoles 4a–m; General Procedure**: The appropriate *N*-styrylbenzamide (**3a**–**m**; 0.015 mmol, 1.0 equiv) was suspended in a 1:1 mixture of anhydrous CH_2Cl_2 and Et_2O (3 mL) and cooled to –78 °C. PIFA (1.2 equiv) and TMSOTf (2.2 equiv) were added and the reaction mixture was stirred at 0 °C until full conversion of the starting material was observed by TLC monitoring. The reaction mixture was diluted with CH_2Cl_2 (3 mL), washed with $NaHCO_3$ (1 M, 3 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc).
Compound 4l: Mp 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 2 H), 7.95 (s, 1 H), 7.78–7.75 (m, 2 H),

7.52–7.47 (m, 3 H), 7.43–7.38 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 152.9, 132.7 (q, *J* = 34.0 Hz), 129.5, 129.4, 129.3, 127.4, 126.3, 124.7, 124.1, 123.6-123.4 (m), 123.1 (q, *J* = 271 Hz). MS (FAB): *m*/*z* = 358.1 $[M+H]^+$. IR: 1736, 1380, 1277, 1130, 943, 901, 843, 767, 730, 681 cm^{-1}. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_9F_6NO$: 358.06611; found: 358.06579.