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COMMUNICATION

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Intramolecular Hydroamidation of *ortho*-Vinyl Benzamides Promoted by Potassium *tert*-Butoxide/*N*,*N*-Dimethylformamide

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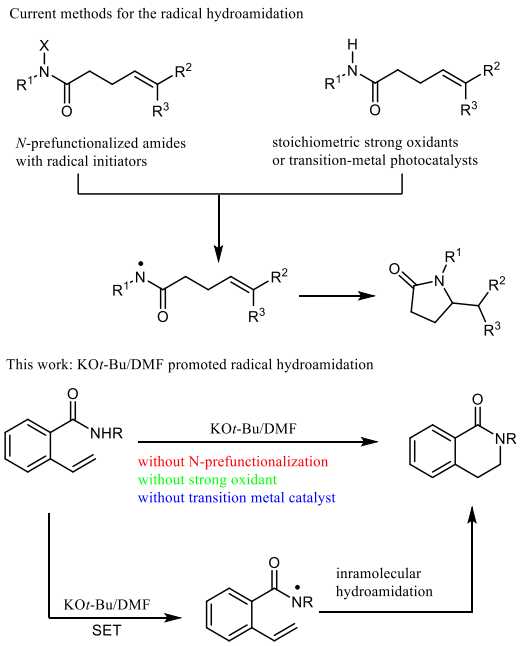
Abstract: An intramolecular hydroamidation of *ortho*-vinyl benzamides had been developed. The reaction was promoted efficiently by potassium *tert*-butoxide and *N*,*N*-dimethylformamide without the need for strong oxidants or transition-metal catalysts. A series of dihydroisoquinolinones and 3-benzylisoindolinones were prepared in good to excellent yields. The new method is operationally simple, scalable, and tolerant of various functional groups.

Keywords: hydroamidation; amidyl radical; potassium *tert*-butoxide; *N*,*N*-dimethylformamide; dihydroisoquinolinone; isoindolinone

Nitrogen-containing compounds are found widely in natural products, pharmaceuticals, agrochemicals, and materials.[1] The development of new methodologies for the selective formation of C-N bonds under mild conditions and in complex molecular settings is of great importance. The hydroamidation of olefins is a powerful approach to C−N bond construction.[2-3] Generally, these reactions were achieved in the presence of various transition-metal catalysts. An alternative strategy via amidyl radical intermediates has made limited progress.[4-5] Conventional methods for the generation of amidyl radicals require either prefunctionalized amides such as *N*-halo-, *N*-nitroso-, or *N*-phenylthioamide derivatives or the use of stoichiometric strong oxidants.[6-7] The direct activation of strong N–H bonds to generate the amidyl radical is more challenging (Scheme 1).[8] Knowles and co-workers recently reported a hydroamidation reaction of amides and olefins catalyzed by iridium photocatalysts via a proton-coupled electron transfer (PCET) pathway. In this process, a weak phosphate base and an iridium photocatalyst in the excited state jointly mediated the homolysis of the anilide N-H bond. The resulting amidyl radical added to the olefin to give the product.[8a-8d] Recently, Xu and co-workers developed an electrocatalytic method for the generation of amidyl radicals from *N*-aryl amides using the inexpensive ferrocene as the redox catalyst. This method was applied for the intramolecular hydroamidation of olefins with good functional group tolerance.[8e] Xiao and co-workers developed a photocatalytic intramolecular hydroamination of *β,γ*-unsaturated hydrazones via *N*-centered hydrazonyl radicals.[9] The radicals were suggested to be generated via the single-electron transfer of the anionic intermediates. Other catalytic activations of N-H bonds to generate nitrogen radicals were developed by the groups of Chiba[8f], Zheng[8g], and Li[8h]. These reactions require stoichiometric oxidants and/or expensive noble-metal catalysts. To overcome these limitations, green and sustainable hydroamidation reactions utilizing non-prefunctionalized amides under redox-neutral conditions are still desirable.

Recently, KO*t*-Bu/DMF has been used in a number of cross-coupling reactions with haloarenes via a single electron transfer pathway.[10] Our group has developed a series of radical reactions of amines, amides and diarylmethanes promoted by KO*t*-Bu/DMF.[11] The corresponding α-amino alkyl radicals, α-amido alkyl radicals and diarylmethyl radicals were proposed to be generated in these reactions. During the study of intramolecular C–N coupling of N′-aryl-2-halobenzohydrazides promoted by KO*t*-Bu, we proposed the generation of *N*-centered benzohydrazide radicals from 2-bromo and 2-iodo substrates.[11g] We speculate that the amidyl radical may be generated from amides promoted by KO*t*-Bu/DMF. The subsequent addition to olefins will give the valuable hydroamidation products (Scheme 1). Herein, we report an intramolecular hydroamidation reaction of *ortho*-vinyl benzamides promoted by KO*t*-Bu/DMF.



Scheme 1. Intramolecular radical hydroamidation of olefins.

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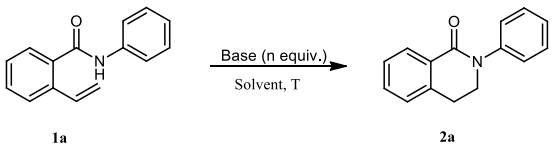
Table 1. Optimization of reaction conditions.[a]



1a 2a

Entry	Base	Solvent	n (equiv.)	T (°C)	Yield (%)[b]
1	KO*t*-Bu	DMF	1.2	90	91
2	KO*t*-Bu	DMF	0.4	90	90
3	NaO*t*-Bu	DMF	0.4	90	50
4	KOMe	DMF	0.4	90	72
5	NaOEt	DMF	0.4	90	51
6	K_2CO_3	DMF	0.4	90	n.d.[c]
7	*n*-BuLi	THF	0.4	–40	n.d.[c]
8	KO*t*-Bu	DMSO	0.4	90	88
9	KO*t*-Bu	DMA	0.4	90	n.d.[c]
10	KO*t*-Bu	THF	0.4	Reflux	n.d.[c]
11	KO*t*-Bu	DMF	0.4	120	99[d]
12	KO*t*-Bu	DMF	0.3	120	99 (90)[d]
13	KO*t*-Bu	DMF	0.2	120	88[d]

[a] *Reaction conditions*: **1a** (0.2 mmol), base (n equiv.), solvent (2.0 mL), at the indicated temperature for 16 h under nitrogen atmosphere unless otherwise indicated.

[b] Determined by GC using *n*-dodecane as the internal standard. The value in the parentheses is the isolated yield after column chromatography.

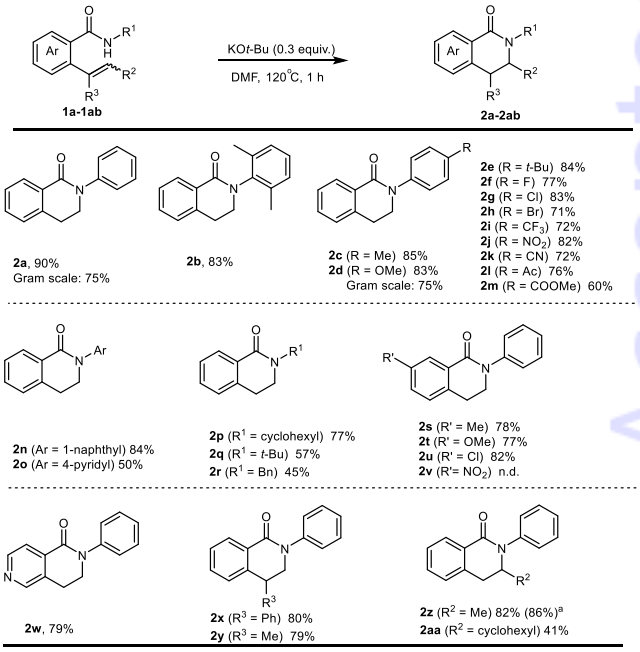
[c] Not detected and the starting material **1a** was recovered.

[d] The reaction time was reduced to 1 h.

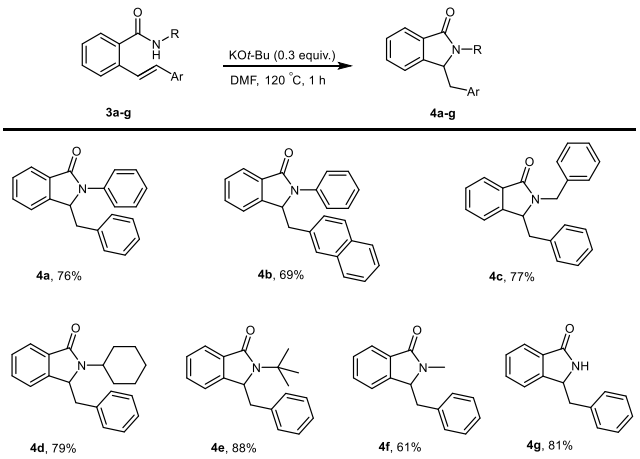
Initially, we examined the reaction of *N*-phenyl-2-vinylbenzamide **1a** in DMF with 1.2 equivalents of KO*t*-Bu at 90 °C. To our delight, 2-phenyl-3,4-dihydroisoquinolinone **2a** was obtained in an excellent yield. The reaction conditions were then optimized and the results are summarized in Table 1. When the KO*t*-Bu loading was reduced to 0.4 equivalent, the reaction gave **2a** in almost the same yield. Other bases such as NaO*t*-Bu, KOMe, and NaOEt were also applicable, but lower yields were obtained (Table 1, entries 3–5). K_2CO_3 was proved to be inefficient (Table 1, entry 6). The reaction with *n*-BuLi in THF was then tested, but no product **2a** was obtained (Table 1, entry 7). DMSO was also found to be a suitable solvent (Table 1, entry 8). Other solvents such as DMA and THF were not applicable (Table 1, entries 9–10). The reaction at the elevated temperature provided a quantitative yield (Table 1, entry 11). The loading of KO*t*-Bu was further examined. The reaction with 0.3 equivalent of KO*t*-Bu also gave the quantitative yield (Table 1, entry 12). A further decrease in the loading of KO*t*-Bu to 0.2 equivalent led to a slight loss of the yield (Table 1, entry 13).

With the optimized reaction conditions in hand, vinylbenzamides **1a–1ab** were examined and the results are summarized in Scheme 2. For a number of *N*-aryl-2-vinylbenzamides, the substitutions with electron-donating groups on *N*-phenyl group were well tolerated. 2,6-Dimethyl (**2b**), 4-methyl (**2c**), 4-methoxyl (**2d**), and 4-*tert*-butyl (**2e**) substituted products were obtained in good yields. The substitutions with 4-halogen (**1f–1h**) were also tolerated well. The corresponding products (**2f–2h**) were obtained in moderate to good yields. The substrates with electron-withdrawing groups such as CF_3 (**1i**), NO_2 (**1j**), CN (**1k**), acetyl (**1l**) and ester (**1m**) afforded the products in moderate to good yields. When the *N*-phenyl group was replaced by a 2-naphthyl group (**1n**), an 84% yield was achieved. The replacement with a pyridyl group (**1o**) was also applicable, but lower yield was obtained. The replacement of *N*-phenyl group with a cyclohexyl group (**1p**) was tolerated well. A 77% yield of **2p** was obtained. Other aliphatic groups such as *tert*-butyl (**1q**) and benzyl (**1r**) were also applicable, however lower yields were observed.[12] The substitutions with electron-donating groups on the benzamide moiety were well tolerated. The products **2s** and **2t** were obtained in good yields. The substitution with 7-chloro (**1u**) was also applicable and **2u** was obtained in a good yield. The reaction of substrate **1v** with a nitro group afforded complicated products. Although complete consumption of **1v** was observed, no expected dihydroisoquinolinone **2v** could be isolated. The decomposition pathways are still elusive so far. The reaction of pyridine derived amide **1w** provided the product **2w** in a 79% yield. The introduction of 1-phenyl or 1-methyl to the vinyl group were also examined. The products **2x** and **2y** were obtained in good yields. The 2-methyl substitution on the vinyl group was tolerated well. The product **2z** was obtained in a good yield. The reaction of 2-cyclohexanyl substituted substrate **1aa** afforded a low yield, probably due to the unfavorable steric hindrance. Furthermore, *o*-allyl benzamide **1ab** was also examined, the product **2z** was obtained in a 86% yield.[13] In this case, the migration of C=C bond might firstly happen to generate **1z**, which underwent the subsequent hydroamidation reaction. To further explore the synthetic potential, the reactions of **1a** and **1d** in gram scale were examined. The products **2a** and **2d** were obtained in good yields.

The stilbene derived amides (**3a–3g**) were also examined (Scheme 3). To our surprise, the reaction of *N*-phenyl-2-(1-phenylprop-1-en-2-yl)benzamide (**3a**) provided a mixture of 5-*exo* and 6-*endo* products with a ratio of 6.5:1 (**4a**:2′).[14] The introduction of 2-phenyl to the vinyl group favored the 5-*exo* pathway and gave the isoindolinone as the major product. When 2-phenyl group was replaced by 2-naphthyl group (**3b**), the 5-*exo* product (**4b**) was obtained exclusively. The changes of the *N*-substituent to benzyl, cyclohexyl, *tert*-butyl and methyl groups



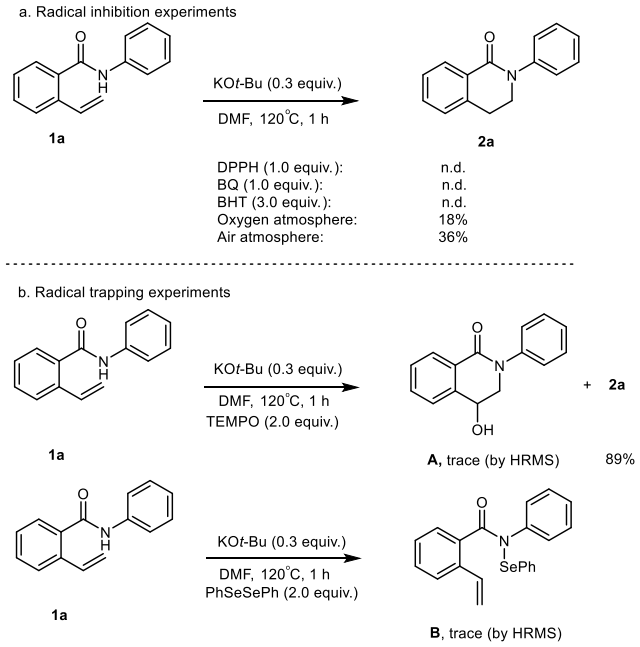
Scheme 2. Intramolecular hydroamidation of **1a-1ab.** *Reaction conditions*: **1a–1ab** (0.2 mmol), KO*t*-Bu (0.06 mmol), DMF (2.0 mL), nitrogen atmosphere, 120 °C, 1 h. Isolated yields. [a] The value in the parentheses is the yield obtained from the reaction of *o*-allyl benzamide **1ab**.



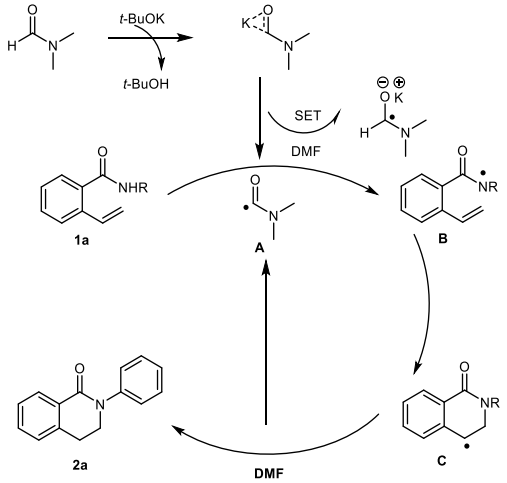
Scheme 3. Intramolecular hydroamidation of stilbene derived amides **3a–3g.** *Reaction conditions*: **3a–3g** (0.2 mmol), KO*t*-Bu (0.06 mmol), DMF (2.0 mL), nitrogen atmosphere, 120 °C, 1 h. Isolated yields.

were tolerated very well. The isoindolinones (**4c–4f**) were obtained in good yields. The *N*-unsubstituted amide is also a suitable substrate. 3-Benzylisoindolinone **4g** was obtained in a good yield. After comparison of the product distributions of **2z**, **2aa**, **4a** and **4b**, we suggest that the stabilization ability of the substituent on vinyl group to the radical intermediate determines the regioselectivity of 5-*exo* and 6-*endo* products. The steric hindrance of the substituent exerts the small effect on the regioselectivity.

To explore the reaction mechanism, radical inhibition experiments were performed (Scheme 4, eq. a). The reaction was completely inhibited in the presence of benzoquinone, DPPH (1,1-diphenyl-2-icrylhydrazyl radical) and BHT (2,6-di-*tert*-butyl-4-methylphenol), and most of **1a** could be recovered. Additionally, the yield was reduced to 18% and 36% respectively under oxygen and air atmosphere.



Scheme 4. Control experiments.



Scheme 5. Proposed reaction mechanism.

Trapping of the radical intermediates with TEMPO and PhSeSePh was attempted (Scheme 4, eq. b). Trace amount of trapping products **A** and B were detected by HRMS (see SI for details). For the former reaction, the product **2a** was obtained in almost the same yield as that in the absence of TEMPO. However, the latter reaction was totally inhibited and 90% of substrate **1a** was recovered. These results are in accordance with a radical reaction pathway, but an anionic reaction pathway cannot be excluded. [15]

Based on the control experiments and our previous studies, [11] a tentative reaction mechanism is proposed (Scheme 5). The carbamoyl radical **A** is generated via the deprotonation of DMF and subsequent single-electron transfer (SET) step.[11c] **A** abstracts a hydrogen atom from **1a** to give the amidyl radical **B**. The intramolecular radical cyclization produces the radical intermediate **C**. **C** abstracts a hydrogen atom from DMF to generate the product **2a** and the carbamoyl radical **A**.

In conclusion, we have developed an intramolecular hydroamidation of *ortho*-vinylbenzamides promoted by KO*t*-Bu/DMF. A series of dihydroisoquinolinones and 3-benzylisoindolinones were synthesized in moderate to excellent yields. This finding provides a simple, practical and transition-metal-free approach for the synthesis of dihydroisoquinolinones and 3-benzylisoindolinones. Further applications of the strategy for the synthesis of other nitrogen heterocycles are currently under way.

Experimental Section

Typical procedure for hydroamidation of *ortho*-vinyl benzamides

To a dried 10 mL reaction tube was added **1a** (44.7 mg, 0.2 mmol), KO*t*-Bu (6.7 mg, 0.06 mmol) and DMF (2.0 mL). The mixture was stirred at 120 °C for 2 h under nitrogen atmosphere. After cooled down to room temperature, the reaction mixture was quenched with water (10.0 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layer was then washed with brine and dried over anhydrous $MgSO_4$. After the evaporation of the solvent under vacuum, the residue was purified by column chromatography (petroleum ether/EtOAc = 5:1) to give **2a** as a white solid (40.2 mg, 90% yield); m.p. 100.7–102.4°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.16 (dd, J = 7.8, 1.4 Hz, 1H), 7.47 (td, J = 7.5, 1.4 Hz, 1H), 7.44–7.35 (m, 5H), 7.29–7.23 (m, 2H), 4.00 (t, J

= 6.4 Hz, 2H), 3.15 (t, *J* = 6.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.2, 143.1, 138.3, 132.1, 129.7, 128.9, 128.8, 127.2, 127.0, 126.3, 125.3, 49.4, 28.7; **HRMS (ESI)** calculated for $C_{15}H_{14}NO$ $(M+H)^+$: 223.0997, found: 223.0996.

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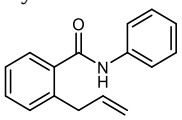
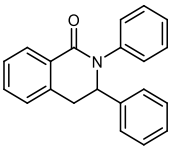
[12] The *N*-unsubstituted amide was also applicable, however the yield was low.

[13] The structure of *o*-allyl benzamide **1ab** is as following.



1ab

[14] The structure of 6-*endo*-product **2′** is as following.



2'

[15] One reviewer suggested that decomposition and side reactions may occur in the radical inhibition experiments with benzoquinone, DPPH, and BHT. The trapping product **A** could arise from the reaction of the benzyl anion intermediate with air. Moreover, the formation of **B** could arise by the electrophilic attack of the amide anion by PhSeSePh. Although we are inclined to a radical reaction pathway based on our accumulated studies on the transformations in KO*t*-Bu/DMF system (ref. 11), we agree with the reviewer that the anionic reaction pathway is also possible and cannot be excluded undoubtedly.

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Intramolecular hydroamidation of *ortho*-vinyl benzamides promoted by potassium *tert*-butoxide

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