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Direct N-vinylation of aryl and hetaryl carboxamides with trimethoxyvinylsilane

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ABSTRACT

A general method for direct N-vinylation of aryl and hetaryl carboxamides with trimethoxyvinylsilane using a copper(II) acetate–TBAF system as catalyst is elaborated. The yield of *N*-vinyl amides depends strongly on the initial amide and nature of the solvent.

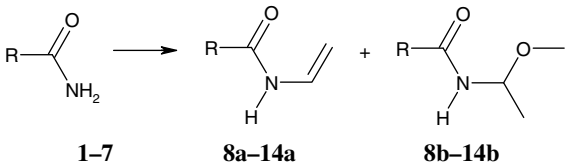
The development of new methods for catalytic C–N bond formation is highly challenging.[1] Notably, copper-promoted nitrogen–carbon bond cross-coupling reactions of amides with organometalloids have received a great deal of attention since initial reports.[2] This method is convenient for the preparation of useful substrates in pharmaceutical chemistry and material sciences. Recently, Lam reported very impressive results for the arylation of hetarylcarboxamides with phenyl trimethoxysilane and tributylphenyltin under mild conditions.[3] Lam's method is based on the α-nitrogen activating effect in the copper(II) acetate-promoted N-arylation. Buchwald's group presented an efficient copper iodide–DMEDA vinylation of amides and imides using various substituted vinyl bromides and iodides.[4] Moreover, according to the literature, no methods are available for direct replacement of amide protons by an unsubstituted vinyl group. *N*-Vinyl benzamide can be obtained by treating vinyl isocyanate with phenylmagnesium bromide,[5a] by thermal decomposition of *N*,*N*′-ethylidene-bis-benzamide at 250 °C[5b] or 4-methyl-2-phenyl-4*H*-oxazol-5-one at 550 °C[5c] or under reduced pressure. Also, *N*-vinyl benzamide was obtained in the reaction of *S*-phenyl-*N*-benzoylthioethanolamine with *O*-mesitylenesulfonylhydroxylamine by elimination of a thiophenol molecule in the presence of potassium carbonate.[5d]

Motivated by the importance of developing direct and facile methods for the synthesis of *N*-vinyl amides using commercially available and inexpensive reagents, we examined the copper-mediated vinylation of primary aryl and hetaryl carboxamides with trimethoxyvinylsilane as the source of a vinyl group. Herein, we report a convenient method for the preparation of *N*-vinylcarboxamides under mild base-free conditions.

In the first step of our investigation, we performed the vinylation of 2-picolinamide in DMF at rt in the presence of various fluorine donors such as CsF/18-crown-6, TBAF, ZnF_2, CuF_2, SmF_3, NdF_3, TbF_3, NH_4BF_4 and NH_4PF_6. According to experimental data, the use of TBAF led to the formation of *N*-vinyl-2-picolinamide (**11a**) in good yield (64%). Also, under the same reaction conditions, compound **11a** was obtained in low yields using ZnF_2 or CuF_2 (10–14%).

Lam's group reported that benzamide on reaction with trimethoxyphenylsilane gave only a 9% yield in DMF of *N*-phenylbenzamide even after heating at 70 °C for 2 days.[3a] Surprisingly, N-vinylation of benzamide proceeded in DMF at room temperature to yield **8a** (36%) (Scheme 1, Table 1). Due to the inconvenience of using DMF as a solvent, we ran the same reaction in dichloromethane and dioxane. It was found that the desired *N*-vinylbenzamide (**8a**) was formed smoothly in 51% yield in CH_2Cl_2 in 10 h at room temperature. Notably, the same reaction in dioxane proceeded much faster at 50 °C (47% yield of **8a**). In our opinion, in the vinylation reaction, the chelating effect of the nitrogen alpha to the amide group is not a necessary requisite as has been reported for the N-arylation reaction of 2-picolinamide with trimethoxyphenylsilane.[3a]

Next, we investigated the influence of substituents on the phenyl ring. Vinylation of 3,4,5-trimethoxybenzamide (**2**) in DMF led to the formation of *N*-vinyl-3,4,5-trimethoxybenzamide (**9a**, entry 5) in a low 17% yield after 5 h of stirring. Vinylation in CH_2Cl_2 gave



1–7 **8a–14a** **8b–14b**

Scheme 1.

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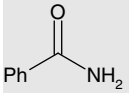
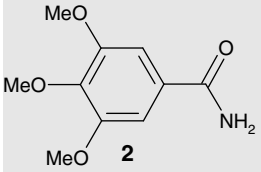
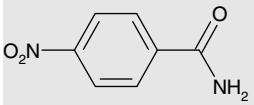
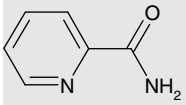
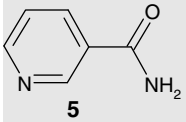
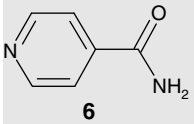
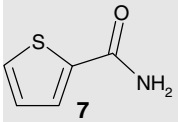
Table 1
N-Vinylation of aryl carboxamides **1–7** with trimethoxyvinylsilane

Amide	Entry	Temperature	Solvent	Time (h)	Vinyl amide (%)	(1-Methoxyethyl) amide (%)
 **1**	1	rt	CH_2Cl_2	10	**8a**, 51	—
	2	rt	DMF	5	**8a**, 36	—
	3	50	Dioxane	2	**8a**, 47	—
 **2**	4	rt	CH_2Cl_2	2	—	**9b**, 40
	5	rt	DMF	5	**9a**, 17	—
	6	rt	DMAc	2	**9a**, 15	**9b**, 33
	7	50	Dioxane	2	—	**9b**, 22
 **3**	8	rt	CH_2Cl_2	2	**10a**, 45	—
	9	rt	DMF	2	**10a**, 34	—
 **4**	10	rt	CH_2Cl_2	10	—	—
	11	rt	DMF	10	**11a**, 64	—
	12	50	Dioxane	10	—	—
 **5**	13	rt	CH_2Cl_2	2	**12a**, 60	**12b**, 21
	14	rt	DMF	2	**12a**, 44	—
	15	50	Dioxane	2	**12a**, 41	**12b**, 4
 **6**	16	rt	CH_2Cl_2	2	**13a**, 57	**13b**, 5
	17	rt	DMF	4	**13a**, 10	—
 **7**	18	rt	CH_2Cl_2	2	**14a**, 7	**14b**, 35
	19	50	DMF	2	**14a**, 30	**14b**, 3
	20	50	Dioxane	5	**14a**, 47	**14b**, 25

3,4,5-trimethoxy-*N*-(1-methoxyethyl)-benzamide **9b** in 40% yield (entry 4).[6] The initially formed *N*-vinyl-3,4,5-trimethoxybenzamide (**9a**) reacts with a methanol molecule, which results from partial trimethoxyvinylsilane polymerization under the reaction conditions, to yield derivative **9b**. The same compound **9b** was observed as the sole product during the vinylation in dioxane (entry 7). According to our experimental data, the use of dimethylacetamide (DMAc) as solvent leads to the formation of a mixture of products **9a** and **9b** (15% and 33%, respectively). No solvent influence on the reaction of 4-nitrobenzamide (**3**) was observed, 4-nitro-*N*-vinyl benzamide (**10a**) was obtained in good yields as a single product (entries 8 and 9). It should be noted that electron-withdrawing substituents on the phenyl ring of benzamide activate the vinyl group for the subsequent addition of methanol; however, in the case of a benzamide with an electron-accepting substituent, the reaction stopped after N-vinylation.

Inspection of the reactivity of pyridine carboxamides showed that picolinamide (**4**), as mentioned before, undergoes reaction with trimethoxyvinylsilane in DMF at room temperature to form the corresponding *N*-vinyl derivative **11a** in 64% yield (entry 11). Our attempts to run this vinylation in dichloromethane or dioxane failed, due to possible formation of an insoluble copper(II) acetate complex with the α-nitrogen of initial compound **4**. Similarly, *N*-vinyl-nicotinamide (**12a**) was obtained in 44% yield as a single product from nicotinamide (**5**) in DMF in 2 h. Notably, vinylation of **5** in CH_2Cl_2 gave the desired vinyl amide **12a** in 60% yield as a mixture with *N*-(1-methoxyethyl)-nicotinamide **12b** (21%). Use of dioxane as the solvent resulted in a 41% yield of *N*-vinylpicolinamide **12a** and only 4% of **12b**. *N*-Vinyl-isonicotinamide (**13a**) was formed in low yield in DMF (10%); however, a mixture of **13a** and *N*-(1-methoxyethyl)-isonicotinamide **13b** was obtained in CH_2Cl_2 (57% and 5% yields, respectively).

Reaction of 2-thiophenecarboxamide (**7**) with trimethoxyvinylsilane in DMF in the presence of copper(II) acetate and TBAF led to the formation of *N*-vinyl-2-thiophenecarboxamide (**14a**) in moderate yield (30%), along with traces of *N*-(1-methoxyethyl)-2-thiophenecarboxamide (**14b**) at 50 °C in 2 h (entry 19).[6] In dichloromethane, the *N*-methoxyethyl derivative **14b** was the major product (35% yield), whereas dioxane gave a mixture of both products **14a** and **14b** (47% and 25% yields, respectively).

The structures of **14a** and **14b** were confirmed unambiguously by X-ray diffraction (Figs. 1 and 2).[7] The molecule of **14a** is planar due to the highly conjugated system. In the crystals of **14a** there are intermolecular NH···O hydrogen bonds. The length of the

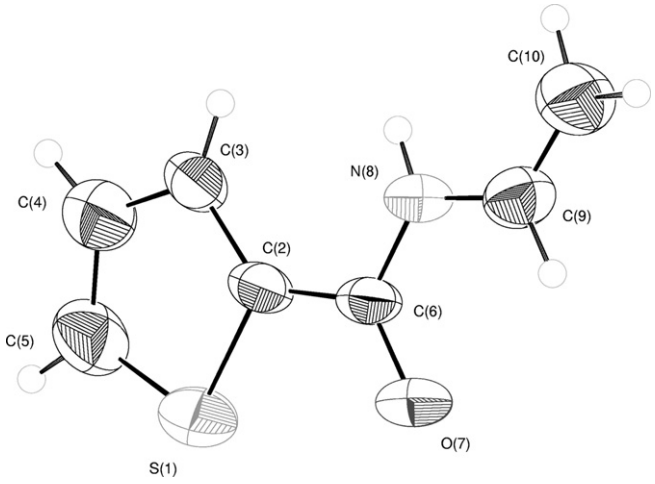


Figure 1. ORTEP molecular structure of thiophene-2-carboxylic acid vinyl amide (**14a**).

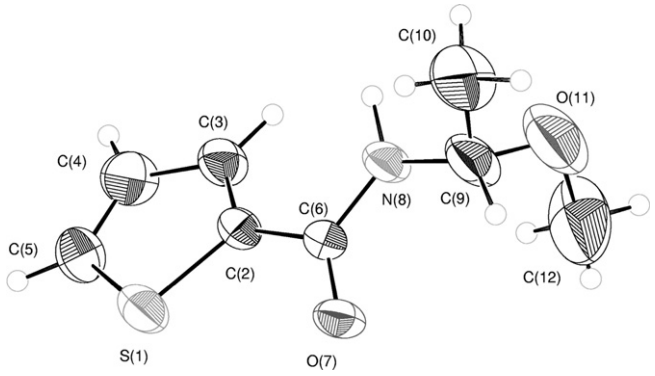


Figure 2. ORTEP molecular structure of thiophene-2-carboxylic acid (1-methoxyethyl)amide (**14b**).

hydrogen bonds is 2.926(3) Å (H···O = 2.13 Å, N–H···O = 163.4°). These hydrogen bonds result in chains being formed in the crystal structure along the crystallographic axis *x*. In the molecules of **14b**, the –CO–NH– group and the C9 carbon atom are in the plane of the thiophene ring. The C10, C9, O11 and C12 atoms lie in the other plane, which is almost perpendicular to the thiophene ring. In the crystals, the intermolecular NH···O type hydrogen bonds form chains along the crystallographic axis *y*. The length of these hydrogen bonds is 2.996(7) Å (H···O = 2.02 Å, N–H···O = 170.0°).

In summary, very simple reaction conditions [$Cu(OAc)_2$, $(MeO)_3$-SiCH=CH_2, TBAF, solvent] have been developed for the direct vinylation of aryl and hetaryl carboxamides. It should be noted that the formation of *N*,*N*-divinyl carboxamides was not observed. It was shown that the yields of the *N*-vinyl amides depend strongly on the structure of the initial amide and solvent nature. Our future efforts will focus on the application of this method to yield various substituted *N*-vinyl amides, and the results will be reported in due course.

Acknowledgement

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6. *General procedure:* To a mixture of arylcarboxamide (1.0 mmol), trimethoxyvinylsilane (2.0 mmol), and copper(II) acetate (1.0 mmol) in 10 mL of the corresponding solvent, 1 M TBAF solution in dioxane (2 mmol) was added. The reaction mixture was stirred and monitored by TLC until complete disappearance of the starting compound. The pure product was isolated by column chromatography on silica gel using chloroform/ethanol mixture 15:1 or 10:1 as eluent. The structures of all the products were confirmed by ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100.6 MHz, $CDCl_3$) NMR data. (a) *N*-vinyl-3,4,5-trimethoxybenzamide (**9a**) ^{1}H NMR: 3.86 (6H, s), 3.87 (3H, s), 4.51 (1H, d, J = 8.7 Hz), 4.79 (1H, dd, J = 0.6 Hz, J = 15.9 Hz), 7.03 (2H, s), 7.11–7.20 (1H, m), 8.06 (1H, br d, J = 9.8 Hz). ^{13}C NMR: 56.3, 60.9, 96.2, 104.6, 128.8, 129.1, 141.3, 153.2, 164.5. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.69; H, 6.38; N, 5.86. (b) 3,4,5-Trimethoxy-*N*-(1-methoxyethyl)-benzamide (**9b**) ^{1}H NMR: 1.43 (3H, d, J = 6.0 Hz), 3.39 (3H, s), 3.87 (6H, s), 3.89 (3H, s), 5.44–5.52 (1H, m), 6.36 (1H, br d, J = 9.6 Hz) 7.02 (2H, s). ^{13}C NMR: 21.7, 55.9, 56.3, 60.9, 78.4, 104.4, 129.2, 141.2, 153.2, 166.8. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.02; H, 7.16; N, 5.22. (c) *N*-Vinyl-2-thiophenecarboxamide (**14a**) ^{1}H NMR: 4.49 (1H, d, J = 8.4 Hz), 4.77 (1H, dd, J = 0.7 Hz, J = 15.8 Hz), 7.21 (1H, dd, J = 1.2 Hz, J = 4.8 Hz), 7.56 (1H, dd, J = 4.0 Hz, J = 4.8 Hz), 7.63 (1H, dd, J = 1.2 Hz, J = 4.0 Hz). ^{13}C NMR: 96.2, 127.8, 127.8, 128.7, 128.8, 129.4, 159.2. Anal. Calcd for C_7H_7NOS: C, 54.88; H, 4.61; N, 9.14; S, 20.93. Found: C, 54.87; H, 4.64; N, 9.11; S, 20.88. (d) *N*-(1-Methoxyethyl)-2-thiophenecarboxamide (**14b**) ^{1}H NMR: 1.42 (3H, d, J = 5.8 Hz), 3.37 (3H, s), 5.41–5.48 (1H, m), 6.37 (1H, br d, J = 8.4 Hz), 7.08 (1H, dd, J = 3.6 Hz, J = 4.9 Hz), 7.51 (1H, dd, J = 1.1 Hz, J = 4.9 Hz), 7.54 (1H, dd, J = 1.1 Hz, J = 3.6 Hz). ^{13}C NMR: 21.7, 55.9, 78.3, 127.7, 128.3, 130.6, 138.5, 161.6. Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56; S, 17.31. Found: C, 51.87; H, 6.02; N, 7.58; S, 17.25.
7. For compounds **14a** and **14b** diffraction data were collected on a Nonius KappaCCD diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The crystal structures of **14a** and **14b** were solved by direct methods[8a,b] and refined by full-matrix least squares.[8c,d] All non-hydrogen atoms were refined anisotropically. Crystal data for **14a**: C_7H_7NOS, orthorhombic, a = 9.9242(3), b = 12.1227(5), c = 12.7055(6) Å; V = 1528.6(1) Å^3, Z = 8, μ = 0.35 mm^{-1}, D_{calc} = 1.331 g cm^{-3}; space group is *Pbca*. A total of 2219 independent reflection intensities ($2\theta_{max}$ = 60°) were collected at room temperature. For structure refinement, 1178 reflections with $I \geqslant 3\sigma(I)$ were used. The final *R*-factor is 0.058. Crystal data for **14b**: $C_8H_{11}NO_2S$, orthorhombic, a = 8.3672(5), b = 9.5519(9), c = 11.8170(6) Å; V = 944.5(1) Å^3, Z = 4, μ = 0.30 mm^{-1}, D_{calc} = 1.303 g cm^{-3}; space group is *Pc*21*a*. A total of 1144 independent reflection intensities ($2\theta_{max}$ = 55°) were collected at room temperature. For structure refinement, 762 reflections with $I \geqslant 2\sigma(I)$ were used. The final *R*-factor is 0.068. For further details, see crystallographic data for **14a** and **14b** deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 676987 and 676988.
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