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A new approach to isoindolinone derivatives by sequential palladium iodide-catalyzed oxidative aminocarbonylation–heterocyclization of 2-ethynylbenzamides

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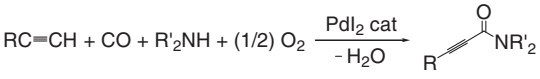
ABSTRACT

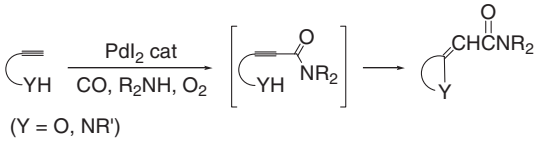
A novel approach to functionalized isoindolinone derivatives **3** is presented. It is based on a cascade process, consisting of PdI_2/KI-catalyzed oxidative monoaminocarbonylation of secondary 2-ethynylbenzamides **1** with nucleophilic secondary amines **2**, followed by intramolecular conjugate addition of the arylamido group to the alkynylamido group of the intermediate alkynylamides. Products have been obtained in high to excellent yields starting from different *N*-alkyl 2-ethynylbenzamides and amines, under relatively mild conditions (100 °C under 40 atm of a 4:1 mixture of CO–air), working in a MeCN–amine mixture (2:1, v/v) for 5–15 h.

PdI_2/KI-catalyzed oxidative monoaminocarbonylation of 1-alkynes with nucleophilic secondary amines is a powerful method for the direct synthesis of 2-ynamides starting from simple building blocks (Eq. 1).[1] When applied to suitably functionalized substrates, it can allow the direct synthesis of carbonylated heterocycles through a sequential process involving oxidative aminocarbonylation of the terminal triple bond followed by intramolecular conjugate addition (Scheme 1).[2]

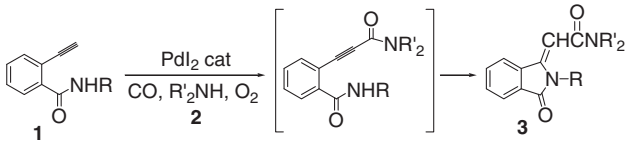


(1)

In this Letter, we report a novel application of this kind of reactivity to the direct synthesis of functionalized isoindolinone derivatives,[3] that are, 3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones **3**, starting from N-substituted 2-ethynylbenzamides **1** (available in four steps from 2-iodobenzoic acid)[4] and nucleophilic secondary amines **2**, according to Scheme 2. To our knowledge, this is the first example of synthesis of this class of compounds by direct carbonylation of acyclic precursors. A non-carbonylative route to 3-[(carbamoyl)methylene]isoindolin-1-ones and 3-[(alkoxycarbonyl)methylene]isoindolin-1-ones, involving an oxidative Pd-catalyzed reaction between *N*-methoxybenzamides and acrylamides or alkyl acrylate, has been recently developed.[5] 3-[(Alkoxycarbonyl)methylene]isoindolin-1-one derivatives were also obtained in low to moderate yields (25–55%) by Pd-catalyzed oxidative alkoxycarbonylation of 2-alkynylbenzamides bearing an internal triple bond, through a completely different reaction course (nucleophilic attack by the amido group to the coordinated triple bond followed by alkoxycarbonylation).[6]



Scheme 1. Formation of carbonylated heterocycles through sequential PdI_2-catalyzed oxidative monoaminocarbonylation of the triple bond—intramolecular conjugate addition.



Scheme 2. Synthesis of 3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones **3** from secondary 2-ethynylbenzamides **1** and nucleophilic secondary amines **2** through sequential PdI_2-catalyzed oxidative monoaminocarbonylation of the triple bond—intramolecular conjugate addition.

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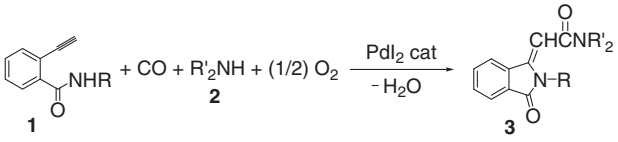
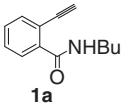
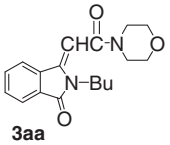
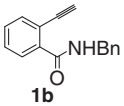
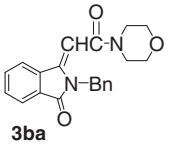
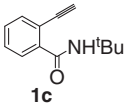
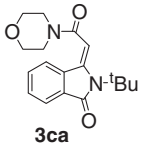
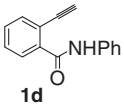
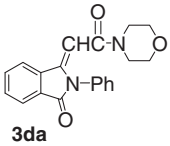
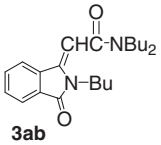
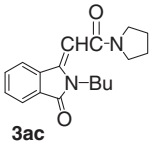
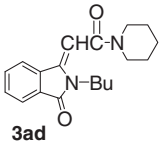
Table 1
Synthesis of 3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones **3** by PdI_2/KI-catalyzed oxidative carbonylation of secondary 2-ethynylbenzamides **1** with nucleophilic secondary amines **2**[a]



Entry	1	2	Time (h)	3	Yield of 3[b] (%)	*Z*/*E* ratio
1	 **1a**	 **2a**	15	 **3aa**	83	2.0
2	 **1b**	**2a**	5	 **3ba**	83	2.2
3	 **1c**	**2a**	15	 **3ca**	94	Only *E*
4	 **1d**	**2a**	8	 **3da**	35	9.7
5	**1a**	Bu_2NH **2b**	15	 **3ab**	81	1.0
6	**1a**	 **2c**	5	 **3ac**	80	1.0
7	**1a**	 **2d**	15	 **3ad**	91	1.0

[a] All reactions were carried out in a 2:1 MeCN–amine mixture as the solvent (substrate concentration = 0.05 mmol of **1** per mL of solvent, 0.7 mmol scale based on **1**) at 100 °C under 40 atm (at 25 °C) of a 4:1 mixture of CO-air, in the presence of PdI_2 (2 mol %) in conjunction with KI (KI/PdI_2 molar ratio = 10). Substrate conversion was quantitative in all cases.
[b] Isolated yield based on starting **1**.

The first substrate we tested was *N*-butyl-2-ethynylbenzamide **1a**, which was allowed to react with morpholine **2a**, CO, and O_2 using a 2:1 MeCN–morpholine mixture as the solvent under 40 atm of a 4:1 mixture of CO–air,[7] in the presence of PdI_2 (2 mol%) in conjunction with KI (KI:PdI_2 molar ratio = 10). Under these conditions, after 15 h a 2.0 *Z*/*E* mixture of 2-butyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one **3aa** was obtained, with a total isolated yield of 83% (Table 1, entry 1).

The aminocarbonylation reaction was then extended to other differently substituted substrates **1b–d** with morpholine **2a** as the nucleophile. Thus, under the same conditions reported above, *N*-benzyl-2-ethynylbenzamide **1b** led to the formation of the corresponding 2-benzyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one **3ba** in 83% yield after 5 h reaction time (*Z*/*E* ratio = 2.2, entry 2). Interestingly, only the *E* isomer of 2-*tert*-butyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one **3ca** was obtained in excellent yield (94%) starting from *N*-*tert*-butyl-2-ethynylbenzamide **1c**, bearing a bulky substituent on the triple bond (Table 1, entry 3). This high stereoselectivity is probably due to the steric effect exerted by the *tert*-butyl group, which directs the dialkylaminocarbamoyl group on the opposite site with respect to the *tert*-butyl substituent. As expected in view of the significantly lower nucleophilicity of a phenyl-substituted amido group, the reaction led to less satisfactory results in the case of

N-phenyl-2-ethynylbenzamide **1d**, which was converted into 2-phenyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one **3da** in only 35% yield (*Z*/*E* ratio = 9.7, Table 1, entry 4). On the other hand, the use of **1a** with other nucleophilic secondary amines, such as dibutylamine **2b**, pyrrolidine **2c**, and piperidine **2d**, led to high to excellent yields (80–91%) of the corresponding 3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones **3ab**, **3ac**, and **3ad**, as shown in Table 1, entries 5–7.[8–11]

In conclusion, we have reported a convenient and direct approach to the synthesis of 3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones **3** by a novel cascade process, involving PdI_2-catalyzed oxidative monoaminocarbonylation of the triple bond of *N*-alkyl-2-ethynylbenzamides **1** followed by 5-*endo*-*dig* intramolecular conjugate addition. Our method represents an interesting example of direct synthesis of functionalized heterocyclic derivatives through the sequential multicomponent assembling of simple building blocks.

Acknowledgments

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3. 3-Methyleneisoindolin-1-one derivatives are an important class of heterocycles. In fact, several molecules incorporating the 3-methyleneisoindolin-1-one core have shown interesting pharmacological activities; for recent examples, see: (a) Abdou, W. M.; Khidre, R. E.; Barghash, R. F. *Synth. Commun.* **2012**, *42*, 1967–1978; (b) Del Olmo, E.; Barboza, B.; Lopez-Perez, J. L.; San Feliciano, A.; Chiaradia, L. D.; Moreno, A.; Benito, A.; Carrero-Lerida, J.; Gonzalez-Pacanowska, D.; Ruiz-Perez, L. M.; Munoz, V.; Gimenez, A.; Martinez, A. R. *Eur. J. Med. Chem.* **2011**, *46*, 5379–5386; (c) Zhu, X.; Greig, N. H.; Yu, Q.-s.; Utsuki, T.; Holloway, H. W.; Lahiri, D. K.; Brossi, A. *Heterocycles* **2004**, *64*, 93–100; (d) Del Olmo, E.; Armas, M. G.; Lopez-Perez, J. L.; Munoz, V.; Deharo, E.; San Feliciano, A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2123–2126; (e) Cid, H. M. B.; Traenkle, C.; Baumann, K.; Pick, R.; Mies-Klomfass, E.; Kostenis, E.; Mohr, K.; Holzgrabe, U. *J. Med. Chem.* **2000**, *43*, 2155–2164.
4. N-substituted 2-ethynylbenzamides **1** were easily prepared from commercially available 2-iodobenzoic acid through conversion into the corresponding acyl chloride followed by amidation with the suitable amine, Sonogashira coupling with trimethylsilylacetylene and deprotection, as reported in the literature: Varela-Fernández, A.; Varela, J. A.; Saá, C. *Adv. Synth. Catal.* **2011**, *353*, 1933–1937.
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7. These conditions (32 atm of CO together with 9 total atm of air, considering that the autoclave was loaded under 1 atm of air) corresponded to 78.0% of CO in air and were outside the explosion limits for CO in air (ca. 16–70% at 18–20 °C and atmospheric pressure, 14.8–71.4% at 100 °C and atmospheric pressure. At higher total pressure, the range of flammability decreases: for example, at 20 atm and 20 °C the limits are ca. 19 and 60%. See: Bartish, C. M.; Drissel, G. M. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Grayson, M., Eckroth, D., Bushey, G. J., Campbell, L., Klingsberg, A., van Nes, L., Eds.; Wiley-Interscience: New York, 1978; Vol. 4, p 775. 3rd ed.
8. Typical procedure for the oxidative carbonylative annulation of N-substituted 2-ethynylbenzamides **1** to 3-(dialkylcarbamoylmethylene)isoindolin-1-ones **3**: A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39×10^{-2} mmol), KI (23.0 mg, 1.39×10^{-1} mmol), and a solution of **1** (0.70 mmol) in a mixture MeCN–amine (MeCN: 9.6 mL; amine **2**: 4.8 mL). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for the required time (see Table 1), the autoclave was cooled, degassed, and opened. When necessary, the mixture was filtered (to remove the solid oxamide by-product deriving from double carbonylation of **2**) and the solid washed with cold Et_2O. The solvent was evaporated, and the products were purified by column chromatography on silica gel (eluent: chloroform for **3aa**; 7:3 hexane–AcOEt for **3ca** and **3da**) or neutral alumina (eluent: 8:2 hexane–AcOEt for **3ba**; 7:3 hexane–AcOEt for **3ab** and **3ad**; 9:1 hexane–AcOEt for **3ac**) to give pure isoindolinones **3**, which were fully characterized by spectroscopic techniques and elemental analysis.[7] The molecular structure of (*Z*)-2-*tert*-butyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one was confirmed by X-ray diffraction analysis, which will be reported in due course.
9. Characterization data for selected products: For **3aa** (mixture of diastereomers *Z*/*E*, *Z*/*E* ratio ca. 2.0, determined by ^{1}H NMR): Pale yellow oil. IR (film): ν = 2960 (m), 2928 (m), 1712 (s), 1684 (vs), 1435 (m), 1400 (w), 1231 (m), 1115 (m), 1040 (w), 769 (m), 699 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.01 [*Z* (m, 1 H, aromatic)], 7.88-7.76 [*Z* (m, 1 H, aromatic) + *E* (m, 1 H, aromatic)], 7.70-7.46 [*Z* (m, 2 H, aromatic) + *E* (m, 3 H, aromatic)], 6.01 [*E* (s, 1 H, = CH)], 5.81 [*Z* (s, 1 H, = CH)], 4.02 [*E* (t, *J* = 7.5, 2 H, NCH_2)], 3.88-3.55 [*Z* (m, 2 H, NCH_2) + *Z* (m, 8 H, morpholine ring) + *E* (m, 8 H, morpholine ring)], 1.73-1.58 [*Z* (m, 2 H, NCH_2CH_2)], 1.58-1.23 [*E* (m, 2 H, NCH_2CH_2) + *Z* (m, 2 H, CH_2CH_3) + *E* (m, 2 H, CH_2CH_3)], 1.01-0.88 [*Z* (m, 3 H, Me) + *E* (m, 3 H, Me)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 166.7, 165.3, 164.8, 142.2, 139.9, 137.2, 134.0, 132.5, 132.2, 130.4, 130.14, 130.07, 128.4, 124.7, 123.4, 123.1, 119.5, 99.5, 96.4, 66.8, 66.7, 66.6, 47.2, 47.1, 42.1, 41.9, 40.7, 39.2, 30.7, 30.3, 20.2, 20.0, 13.9, 13.8; GC-MS (EI, 70 eV): *m*/*z* = 314 (M^+, 12), 271 (5), 228 (100), 210 (11), 200 (48), 186 (11), 172 (32), 159 (12), 158 (12), 146 (6), 130 (34), 114 (4), 102 (8), 89 (7); anal. calcd for $C_{18}H_{22}N_2O_3$ (314.38): C. 68.77; H. 7.05; N, 8.91; found C, 68.84; H, 7.04; N, 8.89. For **3ca** (*E* isomer): Colorless solid. Mp = 145–146 °C IR (KBr): ν = 2979 (w), 2954 (w), 2855 (w), 1708 (s), 1637 (vs), 1433 (m), 1374 (w), 1301 (w), 1232 (m), 1115 (m), 1020 (w), 772 (m), 699 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79-7.71 (m, 2 H, aromatic), 7.56-7.43 (m, 2 H, aromatic), 6.14 (s, 1 H, = CH), 3.86-3.52 (m, 8 H, morpholine ring), 1.78 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 160.9, 141.0, 134.4, 132.3, 130.0, 128.1, 122.99, 122.97, 104.5, 67.3, 66.5, 57.8, 42.1, 40.7, 30.3; GC-MS (EI, 70 eV): *m*/*z* = 314 (M^+, 6), 258 (3), 228 (2), 200 (41), 172 (100), 145 (13), 130 (28), 114 (8), 102 (6), 86 (22); anal. calcd for $C_{18}H_{22}N_2O_3$ (314.38): C. 68.77; H. 7.05; N, 8.91; found C, 68.82; H, 7.03; N, 8.90. For **3ad** (mixture of diastereomers *Z*/*E*, *Z*/*E* ratio ca. 1.0, determined by ^{1}H NMR): Pale yellow oil. IR (film): ν = 2934 (m), 2956 (m), 1713 (s), 1652 (vs), 1470 (m), 1252 (m), 1023 (m), 953 (w), 770 (m), 698 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03-7.96 [*Z* (m, 1 H, aromatic)], 7.86-7.77 [*Z* (m, 1 H, aromatic) + *E* (m, 1 H, aromatic)], 7.69-7.62 [*E* (m, 1 H, aromatic)], 7.61-7.46 [*Z* (m, 2 H, aromatic) + *E* (m, 2 H, aromatic)], 6.04 [*E* (s, 1 H, = CH)], 5.83 [*Z* (s, 1 H, = CH)], 3.99 [*E* (t, *J* = 7.6, 2 H, NCH_2CH_2)], 3.83-3.49 [*Z* (m, 2 H, NCH_2CH_2) + *Z* (m, 4 H, CH_2NCH_2) + *E* (m, 4 H, CH_2NCH_2)], 1.75-1.24 [*E* (m, 10 H, $CH_2CH_2CH_3$ + $CH_2CH_2NCH_2CH_2CH_2$) + *Z* (m, 10 H, $CH_2CH_2CH_3$ + $CH_2CH_2NCH_2$-CH_2CH_2)], 0.96 [*Z* or *E* (t, *J* = 7.3, 3 H, Me)], 0.92 [*E* or *Z* (t, *J* = 7.3, 3 H, Me)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 166.8, 165.0, 164.5, 140.9, 138.7, 137.4, 134.3, 132.3, 132.0, 130.1, 129.9, 124.5, 123.3, 123.1, 119.4, 111.7, 109.4, 101.0, 97.9, 48.0, 47.9, 42.8, 42.5, 40.7, 39.2, 30.7, 30.4, 26.7, 26.4, 25.8, 25.5, 24.58, 24.53, 20.2, 20.1, 13.82, 13.78; GC-MS (EI, 70 eV): *m*/*z* = 312 (M^+, 35), 283 (3), 269 (13), 239 (8), 228 (100), 210 (17), 201 (59), 200 (69), 186 (30), 172 (56), 159 (67), 146 (13), 130 (69), 112 (11), 102 (18), 84 (72); anal. calcd for $C_{19}H_{24}N_2O_2$ (312.41): C, 73.05; H, 7.74; N, 8.97; found C, 73.12; H, 7.72; N, 8.99.
10. The reaction worked to only a very little extent with non-nucleophilic secondary amines, such as hindered amines like diisopropylamine, while primary amines could not be used owing to their transformation into ureas according to a known reactivity.[11]
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