Synthesis of Stereodefined 3-Alkylideneoxindoles by Palladium-catalyzed Reactions of 2-(Alkynyl)aryl Isocyanates with Thiols and Alcohols

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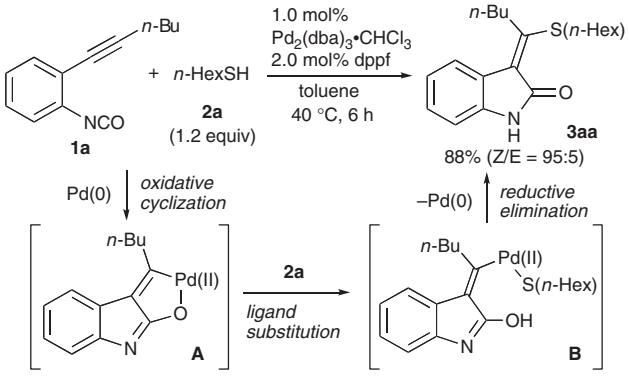
The palladium-catalyzed reactions of 2-(alkynyl)aryl isocyanates with thiols and alcohols caused cyclization to give stereodefined 3-alkylideneoxindoles incorporating sulfanyl and alkoxy groups on the alkylidene unit, respectively.

The 3-alkylideneoxindole-ring system is a privileged structural motif found in a number of pharmaceutically active compounds, including commercially available drugs such as Tenidap[1] and Sutent.[2] In addition, 3-alkylideneoxindoles act as key intermediates in the synthesis of 3-spirooxindole alkaloids and related compounds.[3] Thus, the development of efficient methods to construct 3-alkylideneoxindole structures is in high demand, and recent efforts have been focused on stereoselective synthesis of disubstituted 3-alkylideneoxindoles using transition-metal catalysts.[4] Such approaches work well for the synthesis of a wide variety of 3-alkylideneoxindoles substituted with carbon on the alkylidene unit, e.g., 3-(diarylmethylidene)oxindoles. On the other hand, there are only a few examples of the synthesis of heteroatom-substituted 3-alkylideneoxindoles.[5] We have recently described the palladium-catalyzed cyclization of 2-(alkynyl)aryl isocyanates[6] with amides.[7] The reaction installs a carbon–nitrogen bond onto the alkyne moiety intermolecularly to produce 3-(amidoalkylidene)oxindoles in a stereoselective way. In view of the potential significance of the heteroatom-substituted 3-alkylideneoxindoles, we next tried to incorporate carbon–sulfur and carbon–oxygen linkages onto the alkylidene unit. Herein we report a stereoselective synthesis of 3-(sulfanylalkylidene)- and 3-(alkoxyalkylidene)oxindoles by the palladium-catalyzed reactions of 2-(alkynyl)aryl isocyanates with thiols and alcohols.

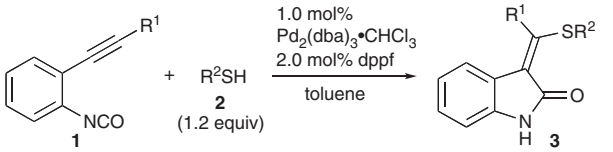
When 2-(1-hexynyl)phenyl isocyanate (**1a**, 1.0 equiv) was treated with hexanethiol (**2a**, 1.2 equiv) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$/dppf [2.0 mol % of Pd; dppf = 1,1′-bis(diphenylphosphino)ferrocene] in toluene at 40 °C, **1a** was completely consumed in 6 h and 3-(sulfanylalkylidene)oxindole **3aa** was obtained as a yellow solid in 88% yield by chromatographic isolation (Z/E = 95:5,[8] Scheme 1). A carbon–sulfur and a carbon–carbon bond were simultaneously introduced across a carbon–carbon triple bond of **1a** in a stereoselective fashion. The product **3aa**, once isolated, was stable and could be kept at room temperature with stereochemical integrity. When subjected to acidic conditions [HCl (5 mol %), toluene, 100 °C, 12 h], however, isomerization readily occurred to give (*E*)-**3aa** (Z/E = 8:92).[9]

The following mechanism which is similar to that we proposed for the reaction with amides[7] is assumed for the stereoselective production of **3aa** from **1a** and **2a**; (i) initially the alkynyl and isocyanato groups both coordinate to a palladium(0) center to promote oxidative cyclization, (ii) the resulting oxapalladacyclic intermediate **A** then undergoes ligand substitution with thiol **2a** to afford the palladium(II) sulfide **B**, (iii) reductive elimination releases the product **3aa**, with the palladium(0) catalyst being regenerated.



Scheme 1.

Table 1. Pd(0)-catalyzed cyclization of **1** with thiols **2**[a]



Entry	**1** (R^1)	**2** (R^2)	T/°C	t/h	**3**	Yield/%[b]
1	**1a** (*n*-Bu)	**2b** (Bn)	70	1	**3ab**	88 (>95:5)
2	**1a** (*n*-Bu)	**2c** (*i*-Pr)	40	12	**3ac**	88 (95:5)
3	**1a** (*n*-Bu)	**2d** (*t*-Bu)	40	6	**3ad**	82 (95:5)[c]
4	**1a** (*n*-Bu)	**2e** (4-$MeOC_6H_4$)	100	2	**3ae**	72 (94:6)
5	**1a** (*n*-Bu)	**2f** (4-ClC_6H_4)	70	1	**3af**	88 (>95:5)[c,d]
6	**1a** (*n*-Bu)	**2g** (Boc-Cys-OMe)	40	24	**3ag**	79 (>95:5)[e]
7	**1b** (*i*-Pr)	**2a** (*n*-Hex)	70	1	**3ba**	73 (77:23)[f]
8	**1c** (*c*-Pr)	**2a** (*n*-Hex)	40	6	**3ca**	97 (38:62)[f]
9	**1d** (Ph)	**2a** (*n*-Hex)	70	1	**3da**	97 (92:8)
10	**1e** (4-$MeOC_6H_4$)	**2a** (*n*-Hex)	40	6	**3ea**	97 (85:15)[f]
11	**1f** (4-$CF_3C_6H_4$)	**2a** (*n*-Hex)	70	1	**3fa**	88 (83:17)
12	**1g** (3-Thienyl)	**2a** (*n*-Hex)	40	6	**3ga**	99 (93:7)

[a]Reactions conducted on a 0.2 mmol scale. [b]Isolated yield. Isomer ratios (Z/E) after chromatographic isolation given in parentheses. [c]1,4-Dioxane (2.0 mL) used. [d]$Pd_2(dba)_3{\cdot}CHCl_3$ (5 μmol) and dppf (10 μmol) used. [e]*N*-(*tert*-Butoxycarbonyl)-L-cysteine methyl ester in 1,4-dioxane (4.0 mL) used. [f]Isomer ratios determined by ^{1}H NMR of crude reaction mixtures; **3ba** (91:9), **3ca** (88:12), **3ea** (>95:5).

Listed in Table 1 are the results obtained with various combinations of 2-(alkynyl)aryl isocyanates **1** and thiols **2**. Not only secondary and tertiary alkanethiols but also benzenethiols reacted well with **1a** to give the corresponding 3-(sulfanylalkylidene)oxindole **3ab**–**3af** in yields ranging from 72 to 88% with high stereoselectivities (Entries 1–5). Even cysteine derivative

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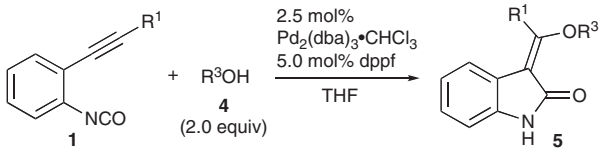
Table 2. Pd(0)-catalyzed cyclization of **1** with alcohols **4**[a]



Entry	**1** (R^1)	**4** (R^3)	T/°C	t/h	**5**	Yield/%[b]
1	**1a** (*n*-Bu)	**4a** (Bn)	40	24	**5aa**	99 (>95:5)
2	**1a** (*n*-Bu)	**4b** (CF_3CH_2)	40	24	**5ab**	95 (94:6)
3	**1a** (*n*-Bu)	**4c** (Me)	40	24	**5ac**	67 (>95:5)
4	**1a** (*n*-Bu)	**4d** (*n*-Pr)	40	24	**5ad**	59 (>95:5)
5	**1a** (*n*-Bu)	**4e** (*c*-Pent)	65	6	**5ae**	32 (>95:5)
6	**1a** (*n*-Bu)	**4f** (TFA-Ser-OMe)	40	12	**5af**	90 (>95:5)[c]
7	**1a** (*n*-Bu)	**4g** (4-$MeOC_6H_4$)	65	6	**5ag**	46 (>95:5)
8	**1a** (*n*-Bu)	**4h** (4-ClC_6H_4)	65	6	**5ah**	44 (>95:5)
9	**1d** (Ph)	**4a** (Bn)	40	24	**5da**	67 (91:9)

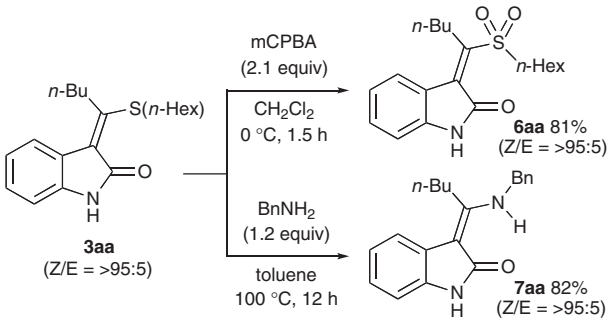
[a]Reactions conducted on a 0.2 mmol scale. [b]Isolated yield. Isomer ratios (Z/E) after chromatographic isolation given in parentheses. [c]0.2 mmol (1.0 equiv) of *N*-(trifluoroacetyl)-L-serine methyl ester used.

2g successfully participated in the reaction (Entry 6). Alkyl groups as well as aryl groups were suitable for the R^1 substituent at the alkyne terminus (Entries 7–12). In some cases lower stereoselectivities were observed, which was ascribed to isomerization of the initially formed (*Z*)-**3** to (*E*)-**3** occurring during the cyclization reaction or purification using silica gel.

This catalytic system was successfully applied to the synthesis of 3-(alkoxyalkylidene)oxindoles by using alcohols instead of thiols as a nucleophile (Table 2). Thus, treatment of **1a** (1.0 equiv) with benzyl alcohol (**4a**, 2.0 equiv) in the presence of $Pd_2(dba)_3$•$CHCl_3$/dppf (5.0 mol % of Pd) in THF at 40 °C in 24 h and the following extractive work-up afforded the product **5aa** in 99% yield (Z/E = >95:5, Entry 1).[10] We assume a mechanism analogous to that of the sulfanylative cyclization shown in Scheme 1. The cyclization reaction of **1a** with various alkanols including the serine derivative **4f** gave the corresponding 3-(alkoxyalkylidene)oxindoles **5ab**–**5af** with high stereoselectivities. A lower yield was observed with a secondary alcohol (Entry 5). The reaction with phenol derivatives **4g** and **4h** required more forcing conditions to afford the products **5ag** and **5ah** in 46 and 44% yield, respectively (Entries 7 and 8).

The synthetic utility of 3-(sulfanylalkylidene)oxindoles was exemplified by further transformations shown in Scheme 2. Treatment of **3aa** (Z/E = >95:5) with mCPBA (2.1 equiv) resulted in the formation of 3-(sulfonylalkylidene)oxindole **6aa** in 81% yield with retention of stereochemistry (Z/E = >95:5). A reaction of **3aa** with benzylamine (1.2 equiv) caused substitution through conjugate addition/elimination to give 3-(aminoalkylidene)oxindole **7aa** in 82% yield.[11] Since an attempted direct aminative cyclization of **1a** with benzylamine failed to occur,[7] the present sequence renders it possible to introduce a nonprotected primary amino group.

In summary, we have found a concise method for the synthesis of 3-(sulfanylalkylidene)- and 3-(alkoxyalkylidene)-oxindoles in a stereoselective way. Various thiols and alcohols could be employed as a coupling partner of 2-(alkynyl)aryl isocyanates.[12] Studies addressing the synthetic scope of the cyclization reaction and the pharmacological properties of the products are ongoing.



Scheme 2.

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