Synthesis of 8-Oxo-3-acetylenic-5,6,7,8-tetrahydroindolizines via Sonogashira Coupling

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Abstract: A selective alkynylation of 3-bromoindolizinone, involving the first copper-free Sonogashira coupling on pyrrole ring, has been developed to afford 8-oxo-3-acetylenic-5,6,7,8-tetrahydroindolizinone.

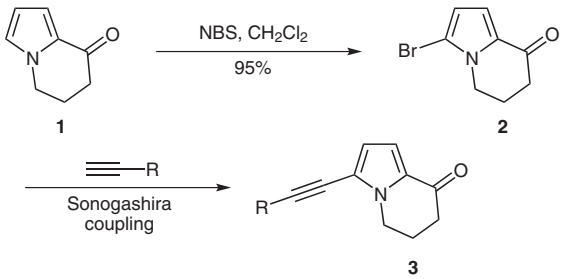
Key words: cross-coupling, pyrrole, palladium, alkynylation, alkaloid

The 8-oxo-5,6,7,8-tetrahydroindolizine skeleton was reported as a key intermediate in the synthesis of indolizidine building blocks[1] and natural indolizidine alkaloids such as the (+)-monomorine,[1g] indolizidine 209D,[1,2] or polygonatines A and B,[1f] and kinganone.[1,3] Recently, 3-substituted 8-oxo-5,6,7,8-tetrahydroindolizines have been identified as inhibitors of Hsp-90, known for anticancer properties.[4] As part of our ongoing research toward 3-substituted 8-oxo-5,6,7,8-tetrahydroindolizines, we recently reported an effective three-step synthesis of 3-aryl-8-oxo-5,6,7,8-tetrahydroindolizines via a palladium-catalyzed arylation or heteroarylation.[5]

Corresponding 3-alkynyl-8-oxo-5,6,7,8-tetrahydroindolizines could be reached via a Sonogashira coupling on the 3-haloindolizinone. This useful method has been widely applied as a key step in natural product and bioactive molecules synthesis. Traditionally, Sonogashira coupling is a palladium-catalyzed cross coupling involving copper(I) as cocatalyst with amine.[6] During the last decades, efforts focused on building such a C–C bond in the absence of copper[7] or palladium.[8] Although Sonogashira coupling is one of the leading 'name' reactions in organic synthesis to introduce acetylenic moiety, only few examples of that kind of coupling were reported on pyrrole ring. Most of them describe the palladium-mediated coupling from iodopyrrole with Cu(I) as cocatalyst.[9]

Furthermore, to the best of our knowledge, only one Sonogashira coupling at the C-2 position of the 2-iodoindolizine core was reported by Kim.[10] To date, no copper-free Sonogashira couplings were described on the pyrrole ring or indolizine core.

Herein, we report a practical access to 3-alkynyl-8-oxo-5,6,7,8-tetrahydroindolizine scaffold via a direct copper-free Sonogashira coupling on a 3-haloindolizinone (Scheme 1).



Scheme 1 Modification of 3-bromoindolizinone

The synthesis of 3-haloindolizinone **2** relies on a procedure based on the regioselective halogenation of the 6,7-dihydro-8(5*H*)-indolizinone **1**. *N*-Bromosuccinimide was chosen as brominating agent. The use of 1.5 equivalents of *N*-bromosuccinimide in dichloromethane gave a mixture of 3-bromoindolizinone and 2,3-dibromoindolizinone in the ratio 65:35. After optimization, halogenation of the starting material gave the 3-bromoindolizinone **2** in 95% yield by using only 1 equivalent of *N*-bromosuccinimide in dichloromethane.[11]

The typical procedure for Sonogashira coupling was initially tested with palladium catalyst and CuI (entry 1, Table 1) at room temperature to afford the corresponding coupling adduct with more than 95% conversion in 86 hours.[12] Palladium-free conditions (entry 2)[13] as well as in presence of palladium on charcoal (entry 3)[14] did not give any conversion. $PdCl_2$ with Ph_3P at room temperature (entry 4) or at 80 °C (entry 5)[15] allowed increasing the conversions until 58%. When the $PdCl_2(PPh_3)_2$ 4 mol% precatalyst was used (entry 6), a conversion of 70% was reached. Finally, the Sonogashira coupling of phenylacetylene on 3-bromoindolizinone with 10 mol% of $PdCl_2(PPh_3)_2$, 1.5 equiv of triethylamine in MeCN at 80 °C gave more than 95% conversion in two hours (entry 7). This procedure represents the first copper-free Sonogashira coupling on pyrrole ring.

Dichlorobis(triphenylphosphine)palladium(II) has been already employed for the direct palladium-catalyzed alkynylation of N-fused heterocycles notably indolizine by Gevorgyan.[16]

When these conditions were performed on the indolizinone with bromophenylacetylene, only 30% conversion was

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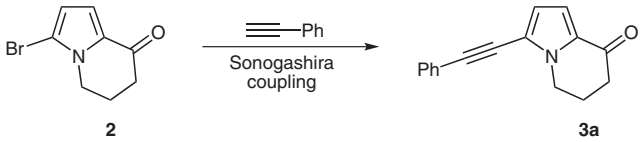
Table 1 Alkynylation of **2** with Phenylacetylene

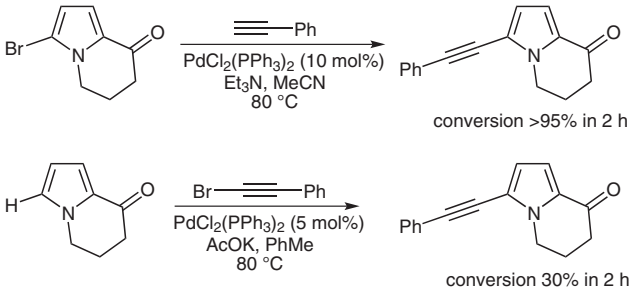


2 **3a**

Entry	Catalyst (mol%)	Cocatalyst (mol%)	Additive (mol%)	Base (equiv)	Solvent	Temp (°C)	Time (h)	Conversion (%)
1	$PdCl_2(PPh_3)_2$ (10)	CuI (5)	–	Et_3N (1.5)	DMF	r.t.	86	>95
2	CuI (2)	–	–	L-Pro (0.06)	DMF	60	24	–
3	Pd/C (1)	–	XPhos (1)	K_2CO_3 (2)	NMP	r.t.	24	–
4	$PdCl_2$ (4)	–	Ph_3P (8)	Et_3N (2)	MeCN	r.t.	24	54
5	$PdCl_2$ (4)	–	Ph_3P (8)	Et_3N (2)	MeCN	80	24	58
6	$PdCl_2(PPh_3)_2$ (4)	–	–	Et_3N (1.5)	MeCN	80	24	71
7	$PdCl_2(PPh_3)_2$ (10)	–	–	Et_3N (1.5)	MeCN	80	2	>95

[a] Determined by GC.

reached (Scheme 2). Thus, our method allowed obtaining the same product with much higher conversion.



Scheme 2 Comparison of two alkynylation methods

The scope of the reaction was finally explored by applying the optimized reaction conditions[17] to the 3-bromoindolizinone with various terminal alkynes (Table 2).

Not surprisingly, electron-donating group on the acetylene moiety gave better conversions and isolated yields. Nevertheless, in methylic ester case (entry 7), the coupling is dramatically penalized. Based on this result, Mårtensson's conditions[18] were tested but did not give any coupling product. Whatever, the aryl-type substituent (entries 1 and 2) or heteroaryl (entry 9), conversions higher than 95% were obtained with isolated yield upper than 80%. Finally, inductive electron-withdrawing groups on terminal alkynes (entries 3 and 8) gave good conversions but difficulties in purification occurred.

Table 2 Pd-Catalyzed Alkynylation of 3-Bromoindolizinone

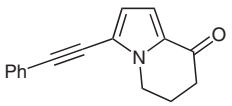
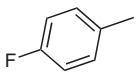
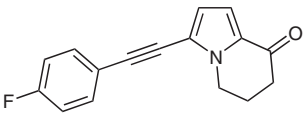
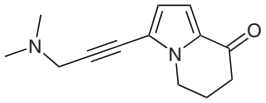
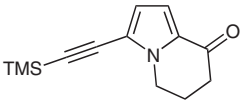
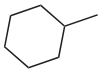
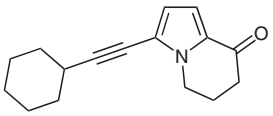
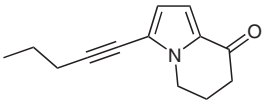
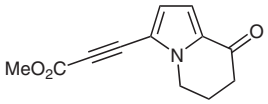
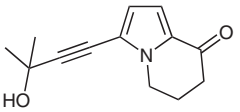
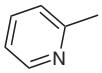
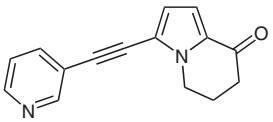
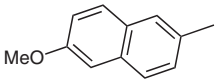
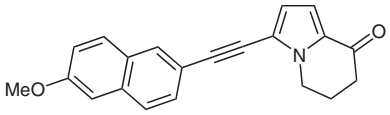
Entry	R	Product		Conversion (%)[a]	Isolated yield (%)
1	Ph		**3a**	>95	82
2			**3b**	>95	90
3	CH_2NMe_2		**3c**	>95	–[b]
4	TMS		**3d**	>95	86

Table 2 Pd-Catalyzed Alkynylation of 3-Bromoindolizinone (continued)

Entry	R	Product		Conversion (%)[a]	Isolated yield (%)
5			**3e**	94	55
6	$(CH_2)_2Me$		**3f**	94	62
7	CO_2Me		**3g**	(–)[c]	–
8			**3h**	>95	60
9			**3i**	>95	83
10			**3j**	85	78

[a] Determined by GC.
[b] Degradation during purification was observed.
[c] Conversion obtained with conditions ref. 18.

In conclusion, a four-step highly divergent strategy from γ-aminobutyric acid and dimethoxytetrahydrofurane was developed allowing the access to 3-acetylenic-8-oxo-5,6,7,8-tetrahydroindolizines which potentially have inhibitive activity on the chaperone Hsp-90. Based on the first copper-free Sonogashira coupling described on pyrrole ring, indolizidines were obtained with global yields between 50% and 81%.

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

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(11) **Synthesis of 3-Bromo-8-oxo-5,6,7,8-tetrahydro-indolizine (2)**
To a solution of 8-oxo-5,6,7,8-tetrahydroindolizine in CH_2Cl_2 (0.12 M) was added NBS (1 equiv) portionwise. The resulting mixture was stirred for 10 min (as monitored by TLC). After removal of the solvent in vacuum, the crude product was purified by column chromatography (cyclohexane–EtOAc, 9:1). A white powder is obtained with 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (m, 2 H), 2.54 (m, 2 H), 4.02 (t, 2 H, *J* = 5.85 Hz), 6.26 (d, 1 H, *J* = 4.32 Hz), 6.96 (d, 1 H, *J* = 4.14 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2 (CH_2), 35.7 (CH_2), 44.4 (CH_2), 109 (C_q), 113.2 (CH), 114.7 (CH), 131.9 (C_q), 131.8 (C_q), 186.5 (CO). HRMS (EI): *m/z* calcd for C_8H_8BrNO: 212.9789; found: 212.9791.

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(17) **General Procedure for Copper-Free Sonogashira Coupling (See Supporting Information)**
To a solution of **2** and $PdCl_2(PPh_3)_2$ (10 mol%) in dry MeCN (0.5 M) under argon were added Et_3N (1.5 equiv) then acetylene (1.2 equiv). The resulting mixture was heated at 80 °C in a sealed tube for the required time (as monitored by GC). The mixture was cooled at r.t. then diluted with CH_2Cl_2. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, concentrated, and finally purified on column chromatography (cyclohexane and cyclohexane–EtOAc = 9:1).
3-(Phenylethynyl)-8-oxo-5,6,7,8-tetrahydro-indolizine (3a)
Yield 82%; yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (m, 2 H), 2.62 (dd, 2 H, *J* = 6.21, 7.53 Hz), 4.22 (dd, 2 H, *J* = 5.64, 7.14 Hz), 6.53 (d, 1 H, *J* = 4.32 Hz), 7.00 (d, 1 H, *J* = 4.14 Hz), 7.37 (m, 3 H), 7.52 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6 (CH_2), 36.4 (CH_2), 43.7 (CH_2), 80.1 (C_q), 95.6 (C_q), 114.1 (CH), 116.1 (CH), 120.1 (C_q), 122.6 (C_q), 128.8 (CH), 129.2 (CH), 131.8 (C_q), 131.8 (CH), 187.2 (CO). HRMS (EI): *m/z* calcd for $C_{16}H_{13}NO$: 235.0997; found: 235.0995.

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