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Short Communication

Palladium-catalyzed aminobenzannulation during Sonogashira couplings using *o*-bromoacetophenone

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Abstract

The palladium-catalyzed coupling of alkynes with *o*-bromoacetophenone has been investigated. If this reaction is conducted in an amine solvent and is allowed to proceed for a lengthy reaction time, a benzannulation process, resulting in an aminonaphthalene derivative, follows the expected Sonogashira coupling. The scope and limit of this reaction has been briefly investigated.

Keywords: Benzannulation; Sonogashira coupling; Palladium catalysis; Alkynylation; Cyclization; Cycloaddition; *o*-Bromoacetophenone; Aminonaphthalenes

1. Introduction

As part of our continued interest in the generation of isobenzofurans through the coupling of *o*-alkynylbenzoyl systems with Fischer carbene complexes [1], we have examined the Sonogashira coupling of *o*-halobenzoyl derivatives with terminal alkynes. This is the primary synthetic route we utilize for preparation of this class of compounds. In most cases, this reaction provides a high-yielding route to these compounds, however we noticed that in the coupling of *o*-bromoacetophenone (**1A**, Scheme 1) with 1-hexyne in diethylamine [2], the expected ketone derivative **2A** is frequently accompanied by aminonaphthalene derivative **3A**. In this manuscript, we will discuss the mechanism and optimization of the reaction leading to **3A**. Similar cyclizations of *o*-alkynylacetophenone derivatives to phenols have been reported [3], however direct formation of aminonaphthalene **3A** from ketone **1A** represents a net aminobenzannulation reaction via a [4 + 2] cycloaddition sequence. Development of a general aminobenzannulation procedure using the Dötz reaction as a basis is a longstanding goal of many research efforts [4].

2. Results and discussion

In the coupling of ketone **1A** with 1-hexyne, several observations were noted concerning the distribution of alkyne–ketone **2A** and naphthalene **3A**. The naphthalene derivative was more prevalent at longer reaction times, and was the exclusive product if the reaction proceeded for 3 days at 55 °C (reflux temperature). If alkyne–ketone **2A** was subjected to diethylamine and the Sonogashira catalyst, naphthalene **3A** was also produced. Subjection of alkyne–ketone **2A** to diethylamine did not result in any of the naphthalene derivative. Formation of the enamine from the ketone followed by treatment with the palladium catalyst in diethylamine also led to formation of the naphthalene derivative. Based on these observations, the mechanism depicted in Scheme 2 has been proposed for the conversion of alkyne–ketone **2A** to aminonaphthalene **3A**. The key step in this transformation involves palladium-catalyzed

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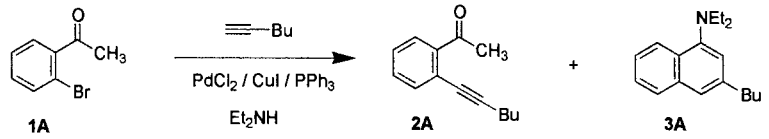
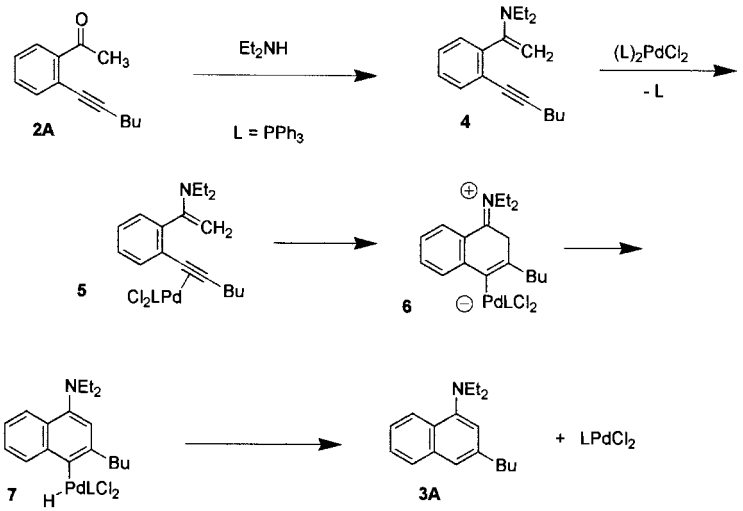
addition of the enamine to the alkyne [5] followed by proton transfer to palladium and reductive elimination.

A series of *o*-bromophenyl ketones were treated with alkynes and amines under the optimal conditions for aminobenzannulation (Table 1). Ketone **1A** led to the respective naphthylamines **3A** and **3B** (entries A and B) in excellent yield upon treatment with 1-hexyne and the Sonogashira catalyst system in either diethylamine or pyrrolidine for a 72 h period. The cyclization approach (entry C) to compound **3A** was similarly efficient. Unfortunately, no other case resulted in a successful benzannulation reaction. The tandem Sonogashira–benzannulation sequence (**1** + alkyne going to **3**) failed using either trimethylsilylacetylene or phenylacetylene as the alkyne component (entries F and I), and using any ketone derivatives where $R^1 \neq H$ (entries D and E). Simple cyclization of *o*-alkynylacetophenone derivatives (**2** going to **3**) also failed for all cases where

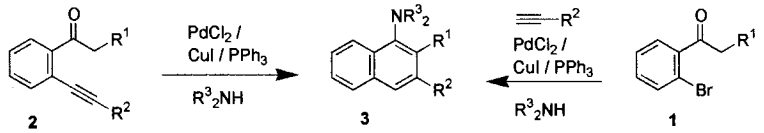


Scheme 1.



Scheme 2.

Table 1
Synthesis of aminonaphthalenes (**3**) from *o*-bromoacetophenone (**1**) or *o*-alkynylacetophenone (**2**) derivatives in amine solvents at reflux temperature



Entry	R^1	R^2	R^3	Reactant combination	Yield **3** (%)
A	H	Bu	Et	**1** + Alkyne + amine + Pd	92 (**3A**)
B	H	Bu	$R^3_2 = -(CH_2)_4-$	**1** + Alkyne + amine + Pd	82 (**3B**)
C	H	Bu	Et	**2** + Amine + Pd	86 (**3A**)
D	*n*-Pr	Bu	Et	**1** + Alkyne + amine + Pd	0
E	Ph	Bu	$R^3_2 = -(CH_2)_4-$	**1** + Alkyne + amine + Pd	0
F	H	TMS	$R^3_2 = -(CH_2)_4-$	**1** + Alkyne + amine + Pd	0
G	H	TMS	$R^3_2 = -(CH_2)_4-$	**2** + Amine + Pd	0
H	H	H	$R^3_2 = -(CH_2)_4-$	**2** + Amine + Pd	0
I	H	Ph	Et	**1** + Alkyne + amine + Pd	0
J	H	Ph	Et	**2** + Amine + Pd	0

$R^1 \neq H$ or $R^2 \neq$ alkyl (entries G, H, and J). In entries D–J, *o*-alkynylacetophenone derivative **2** was the major product from failed benzannulation using **1**, while sharing material recovery was noted in cyclizations involving *o*-alkynylacetophenone derivatives **2** as the starting material.

3. Conclusions

In summary, a novel synthetic route to aminonaphthalenes using the coupling of *o*-bromoacetophenone with monoalkyl acetylenes has been presented. The reaction appears to be limited to acetophenone derivatives and monoalkylacetylenes, which leads to the formation of 3-alkyl-1-aminonaphthalene systems in high yield.

4. Experimental

4.1. Naphthalene *3A*

A mixture of *o*-bromoacetophenone (2 ml, 14.8 mmol), 1-hexyne (2.3 ml, 17.8 mmol), palladium chloride (0.048 g, 0.27 mmol), triphenylphosphine (0.120 g, 0.46 mmol), cuprous iodide (0.160 g, 0.84 mmol) in diethylamine (50 ml) was heated at reflux for a 72 h period. The mixture was cooled to 25 °C, filtered through silica gel using ether to wash the filter pad, and the solvent was removed on a rotary evaporator. The residue after evaporation was dissolved in ether and extracted three times with 1 M aqueous HCl. The combined aqueous layers were neutralized with 1 M aqueous NaOH solution and extracted three times with ether. The combined ether layers were washed with saturated aqueous sodium chloride solution and dried over Na_2SO_4. The solvent was removed on a rotary evaporator and the residue after evaporation was purified by flash chromatography on silica gel using 6:1 hexane:EtOAc as eluent. After removal of the chromatography solvent on a rotary evaporator, a colorless oil identified as aminonaphthalene derivative **3A** (3.47 g, 92%) was obtained. ^{1}H-NMR ($CDCl_3$): δ 8.22 (m, 1H), 7.69 (m, 1H), 7.41 (m, 2H), 7.31 (s, 1H), 6.97 (s, 1H), 3.19 (q, 4H, $J = 7.1$), 2.74 (t, 2H, $J = 6.6$), 1.66 (quintet, 2H, $J = 6.6$), 1.37 (sextet, 2H, $J = 6.6$), 1.03 (t, 6H, $J = 7.1$), 0.93 (t, 3H, $J = 6.6$); ^{13}C-NMR ($CDCl_3$): δ 147.6, 139.9, 134.9, 129.6, 127.5, 125.5, 124.1, 124.0, 121.7, 119.4, 47.6, 35.9, 33.4, 22.3, 13.9, 12.2; EIMS: 255 (M, 49), 240 (100), 183 (12), 168 (11); HRMS: Anal. Found: 255.1998. Calc. for $C_{18}H_{25}N$: 255.1987.

4.2. Naphthalene *3B*

A procedure identical to **3A** was employed using pyrrolidine as a substitute for triethylamine and conducting the reaction at reflux (87 °C). From *o*-bromoacetophenone (0.597 g, 3.00 mmol), 1-hexyne (0.312, 3.80 mmol), palladium chloride (0.018 g, 0.10 mmol), triphenylphosphine (0.053 g, 0.20 mmol), cuprous iodide (0.039 g, 0.20 mmol) in pyrrolidine (30 ml), a colorless oil identified as aminonaphthalene derivative **3B** (0.63 g, 82%) was obtained. ^{1}H-NMR ($CDCl_3$): δ 8.17 (dd, 1H, $J = 9.0, 1.5$), 7.74 (dd, 1H, $J = 7.1, 1.6$), 7.39 (m, 2H), 7.26 (s, 1H), 6.85 (s, 1H), 3.38 (br t, 4H, $J = 6.5$), 2.75 (t, 2H, $J = 6.6$), 2.03 (m, 4H), 1.72 (quintet, 2H, $J = 6.6$), 1.43 (sextet, 2H, $J = 6.6$), 0.98 (t, 3H, $J = 6.6$); ^{13}C-NMR ($CDCl_3$): δ 147.4, 140.3, 135.1, 127.7, 126.7, 125.4, 124.4, 123.3, 119.8, 113.1, 52.6, 36.1, 33.4, 24.7, 22.4, 13.9; EIMS: 253 (m, 100), 224 (30), 211 (96), 210 (62), 182 (24), 181 (21), 180 (34), 167 (50), 141 (64); HRMS: Anal. Found: 253.1822. Calc. for $C_{18}H_{23}N$: 253.1830.

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