Journal of Organometallic Chemistry 696 (2011) 352–356

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

$ZnCl_2$-catalyzed [4 + 2] benzannulation of 2-ethynylbenzaldehydes with alkynes: Selective synthesis of naphthalene derivatives

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ARTICLE INFO

Article history:
Received 26 July 2010
Received in revised form
26 September 2010
Accepted 27 September 2010
Available online 7 October 2010

Keywords:
$ZnCl_2$
[4 + 2] Benzannulation
Alkynylbenzaldehyde
Alkyne
Naphthalene

ABSTRACT

Zn-catalyzed [4 + 2] benzannulation of 2-ethynylbenzaldehydes with alkynes is described for the selective synthesis of naphthalene derivatives. In the presence of $ZnCl_2$, a variety of 2-ethynylbenzaldehydes underwent the [4 + 2] benzannulation reactions with alkynes to selectively afford the corresponding naphthalene derivatives in moderate to good yields.

1. Introduction

The synthesis of naphthalene rings is of continuingly interesting in the field of organic chemistry because these compounds play important roles in materials science and pharmaceutical industries [1–21]. Although diverse synthetic approaches toward naphthalene compounds have been developed [1–54], versatile and efficient methodologies to construct these compounds with selective control of substitution patterns using readily accessible building blocks are still needed. Recently, Lewis acid-catalyzed [4 + 2] benzannulations of 2-ethynylbenzaldehydes with unsaturated compounds (alkynes, alkenes and enols) have been proven as a powerful alternative to naphthalenes [45–54]. However, only a few papers have been reported on these benzannulation transformations, particularly benzannulation between 2-ethynylbenzaldehydes and alkynes [51–54]. Moreover, the catalysts are restricted to some highly expensive Lewis acids, such as $AuCl_3$ and $Cu(OTf)_3$ [45–54]. In 2002, Asao and Yamamoto firstly described an efficient route to naphthyl ketone derivatives through gold-catalyzed [4 + 2] cycloaddition of *o*-alkynylbenzaldehydes with alkynes (Scheme 1) [51–53]. Subsequently, they found that with the aid of CF_2HCOOH $Cu(OTf)_2$ was an effective catalyst for this [4 + 2] benzannulation and shifted the selectivity toward the debenzoylated naphthalenes through the cleavage of a carbon–carbon triple bond [54]. However, both the debenzoylated naphthalenes (major) and naphthyl ketones (minor) were observed in the presence of the other additives (such as H_2O, MeOH, HCO_2H, CH_3CO_2H or CF_3CO_2H) or without additives [54]. Thus, the development of some new routes, including the use of inexpensive Lewis acids under additive-free conditions for the [4 + 2] benzannulation is interesting. Here, we report a practical protocol for the synthesis of the debenzoylated naphthalenes by Zn-catalyzed benzannulation of 2-ethynylbenzaldehydes with alkynes without the requirement of additives (Scheme 1) [50,55–64].

2. Experimental

2.1. General remarks

NMR spectroscopy was performed on a Bruker-300 spectrometer operating at 300 MHz (^1H NMR) and 75 MHz (^{13}C NMR). TMS (tetramethylsilane) was used an internal standard and CD_3Cl was used as the solvent. Mass spectrometric analysis was performed on GC–MS analysis (SHIMADZU GCMS-QP2010).

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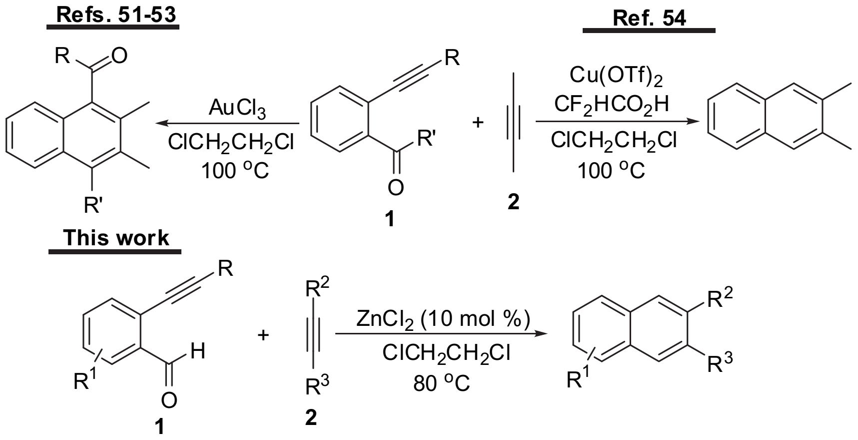
doi:10.1016/j.jorganchem.2010.09.062



Scheme 1. Lewis acids-catalyzed [4 + 2] benzannulations of 2-ethynylbenzaldehydes with alkynes.

2.2. Typical experimental procedure for the $ZnCl_2$-catalyzed [4 + 2] benzannulation of 2-alkynylbenzaldehyde with alkynes

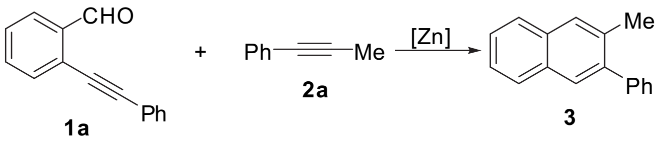
To a Schlenk tube were added 2-alkynylbenzaldehyde **1** (0.2 mmol), alkyne **2** (1 equiv), $ZnCl_2$ (10 mol%), and $ClCH_2CH_2Cl$ (3 mL). Then the tube was charged with argon, and was stirred at 80 °C (oil bath temperature) for the indicated time until complete consumption of starting material as monitored by TLC and GC–MS analysis. After the reaction was finished, the reaction mixture was cooled to room temperature, diluted in diethyl ether, and washed with brine. The aqueous phase was re-extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the desired product.

3. Results and discussion

The reaction between 2-(2-phenylethynyl)benzaldehyde (**1a**) and 1-phenylpropyne (**2a**) was chosen as a model reaction to optimize the reaction conditions, and the results are summarized in Table 1. Initially, a series of zinc salts, including ZnF_2, $ZnCl_2$, $ZnBr_2$, ZnI_2 and $Zn(acac)_2$, were investigated (entries 1–5). We found that ZnF_2 had no effect on the reaction of aldehyde **1a** with alkyne **2a** (entry 1). To our delight, the reaction was carried out successfully using $ZnCl_2$, $ZnBr_2$ or ZnI_2 Lewis acids, and $ZnCl_2$ was the most effective in terms of yields (entries 2–4). However, $Zn(acac)_2$ was inert for the benzannulation reaction (entry 5). It was disclosed that the yields of the desired product **3** were reduced when the loading of $ZnCl_2$ was increased to 20 mol% or decreased to 5 mol% (entries 6 and 7). Subsequently, three other solvents, DMF, dioxane and toluene, were evaluated, and they were found to disfavor this benzannulation reaction: a trace amount of the desired product **3** was observed in either DMF or dioxane, and in toluene only 35% yield was isolated (entries 8–10). Among the effect of the reaction temperature examined, it turned out that at room temperature the activities of substrates **1** and **2** were lowered (entry 11), and the reaction at 100 °C provided the identical results to those of 80 °C (entry 12). Other Lewis acids, including $YbCl_3$, $Yb(OTf)_3$, $InCl_3$ and $GaCl_3$, were tested; however, they displayed less efficiency for the reaction (enries 13–16).

With the optimal reaction conditions in hand, the scopes of both 2-alkynylbenzaldehydes and alkynes for the benzannulation reaction were explored (Table 2). A variety of alkynes **2b**–**2j**, either internal or terminal alkynes, were initially investigated by reaction with 2-(2-phenylethynyl)benzaldehyde (**1a**) in the presence of $ZnCl_2$. To our delight, internal alkynes **2b**–**2e**, bearing aryl or/and aliphatic groups, successfully underwent the annulation reaction with **1a** and $ZnCl_2$ in moderate to good yields (entries 1–4). For instance, substrate **2d** with a thiophen-2-yl and a *n*-hexyl group was treated with **1a** and $ZnCl_2$ in 60% yield (entry 3). It was surprised to observe that phenyl(2-phenylethynyl)sulfane (**2e**) reacted with **1a** did not yield the expected 2-phenyl-3-phenylsulfanylnaphthelene [45], but the dephenylsulfanyl 2-phenylnaphthalene **7** in 84% yield (entry 4). However, electron-poor alkyne **2f** was not suitable under the same conditions (entry 5). We were interesting to disclose that terminal alkynes displayed higher activity than internal alkynes in term of yields. Among terminal alkynes **2g**–**2j**, substituents, such as phenyl, $4\text{-}NO_2C_6H_4$, *n*-hexyl and *t*-butyl groups, were perfectly tolerated (entries 6–9).

Table 1
The [4 + 2] benzannulation reaction of 2-(phenylethynyl)benzaldehyde (**1a**) with prop-1-ynylbenzene (**2a**)[a]



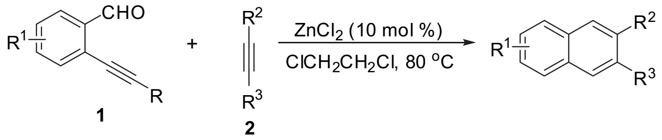
Entry	[Zn]	Solvent	T (°C)	Isolated yield (%)
1	ZnF_2	$ClCH_2CH_2Cl$	80	trace
2	$ZnCl_2$	$ClCH_2CH_2Cl$	80	86
3	$ZnBr_2$	$ClCH_2CH_2Cl$	80	81
4	ZnI_2	$ClCH_2CH_2Cl$	80	79
5	$Zn(acac)_2$	$ClCH_2CH_2Cl$	80	trace
6[b]	$ZnCl_2$	$ClCH_2CH_2Cl$	80	77
7[c]	$ZnCl_2$	$ClCH_2CH_2Cl$	80	65
8	$ZnCl_2$	DMF	80	trace
9	$ZnCl_2$	dioxane	80	trace
10	$ZnCl_2$	toluene	80	35
11	$ZnCl_2$	$ClCH_2CH_2Cl$	rt	50
12	$ZnCl_2$	$ClCH_2CH_2Cl$	100	83
13	$YbCl_3$	$ClCH_2CH_2Cl$	80	trace
14	$Yb(OTf)_3$	$ClCH_2CH_2Cl$	80	6
15	$InCl_3$	$ClCH_2CH_2Cl$	80	11
16	$GaCl_3$	$ClCH_2CH_2Cl$	80	10

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), and [Zn] (10 mol %) in solvent (3 mL) for 36 h.

[b] $ZnCl_2$ (20 mol%).

[c] $ZnCl_2$ (5 mol%) for 48 h.

Table 2
$ZnCl_2$-catalyzed benzannulation of 2-ethynylbenzaldehydes (**1**) with alkynes (**2**)[a]



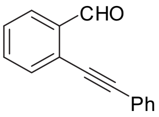
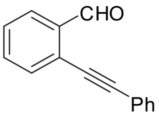
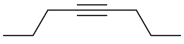
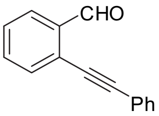
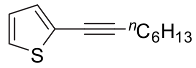
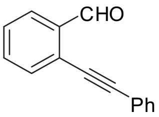
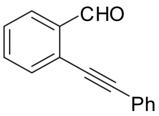
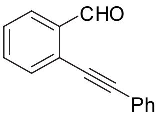
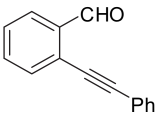
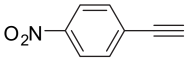
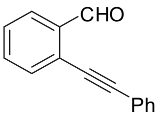
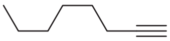
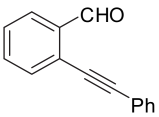
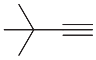
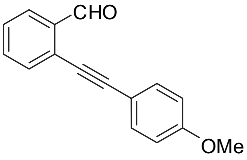
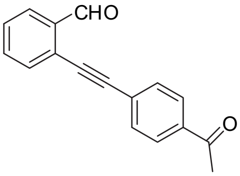
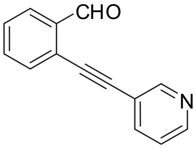
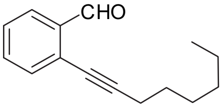
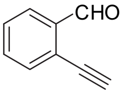
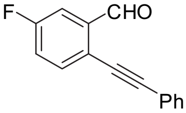
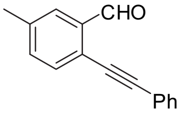
Entry	Substrate **1**	Alkyne **2**	Time (h)	Isolated yield (%)
1	 (**1a**)	$Ph-C\equiv C-Ph$ (**2b**)	20	54 (**4**)
2	 (**1a**)	 (**2c**)	20	51 (**5**)
3	 (**1a**)	 (**2d**)	20	60 (**6**)
4	 (**1a**)	$Ph-C\equiv C-S-Ph$ (**2e**)	11	84 (**7**)
5	 (**1a**)	$MeO_2C-C\equiv C-CO_2Me$ (**2f**)	24	trace (**8**)
6	 (**1a**)	$Ph-C\equiv CH$ (**2g**)	12	81 (**7**)
7	 (**1a**)	 (**2h**)	16	70 (**9**)
8	 (**1a**)	 (**2i**)	12	61 (**10**)
9	 (**1a**)	 (**2j**)	12	53 (**11**)

Table 2 (*continued*)

Entry	Substrate **1**	Alkyne **2**	Time (h)	Isolated yield (%)
10	 (**1b**)	Ph—≡— (**2a**)	10	45 (**3**)
11	 (**1c**)	Ph—≡— (**2a**)	8	86 (**3**)
12	 (**1d**)	Ph—≡— (**2a**)	20	31 (**3**)
13	 (**1e**)	Ph—≡— (**2a**)	11	70 (**3**)
14	 (**1f**)	Ph—≡— (**2a**)	20	15 (**3**)
15	 (**1g**)	Ph—≡— (**2a**)	10	87 (**12**)
16	 (**1h**)	Ph—≡— (**2a**)	9	89 (**13**)

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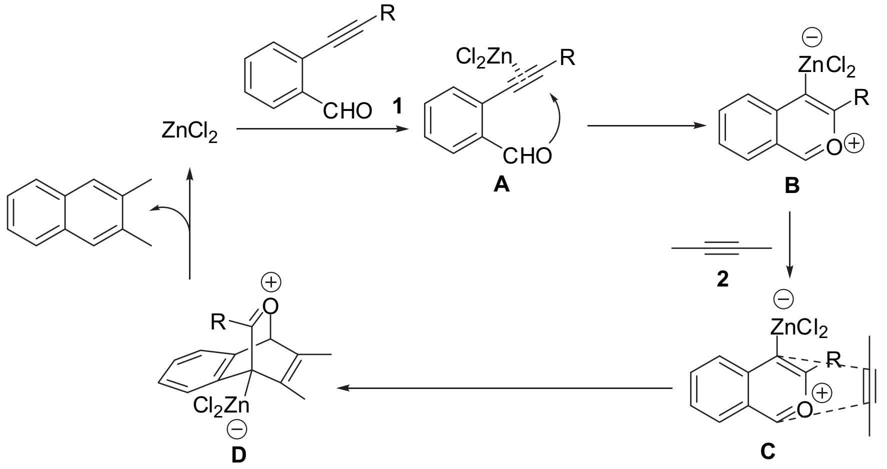
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $ZnCl_2$ (10 mol%), in $ClCH_2CH_2Cl$ (3 mL) at 80 °C.

Subsequently, a number of 2-alkynylbenzaldehydes **1b**–**1h** were examined for the reaction with alkyne **2a** under the optimal conditions (entries 10–16). Substituents, 4-$MeOC_6H_4$, 4-CH_3CO C_6H_4, and *n*-hexyl groups, at the terminal alkyne on the 2-ethynylbenzaldehyde moiety were consistent with the optimal conditions (entries 10, 11, and 13). The desired product **3** was still isolated in 31% from the reaction of pyridin-3-yl-containing substrate **1d** with alkyne **2a** and $ZnCl_2$ (entry 12). However, 2-ethynylbenzaldehyde (**1f**) was less active for the reaction (entry 14). Gratifyingly, the optimal conditions were compatible with both F- and Me-substituted benzaldehydes **1g** and **1h**, providing the corresponding product **12** and **13** in good yields (entries 15 and 16).

A possible mechanism as outlined in Scheme 2 was proposed on the base of the earlier reported mechanism [45–54]. The coordination of the triple bond of 2-ethynylbenzaldehyde **1** to $ZnCl_2$ enhances the electrophilicity of alkyne (intermediate **A**), followed by the nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne among intermediate **A** affords intermediate **B**. The Diels–Alder reaction of **B** with an alkyne **2** takes place leading to intermediate **D** [54]. Finally, the bond rearrangement of intermediate **D** yields the decarbonylated naphthalenes and regenerates the active Zn catalyst species. The activity of Zn salts is $ZnCl_2 > ZnBr_2$, $ZnI_2 > ZnF_2$, $Zn(acac)_2$ in terms of yields, and the reason is that $ZnCl_2$ is more acidic than the other Zn salts.



Scheme 2. Possible mechanism.

4. Conclusion

In summary, we have developed a practical $ZnCl_2$-catalyzed [4 + 2] benzannulation method for the synthesis of the decarbonylated naphthalenes. In the presence of $ZnCl_2$, a variety of 2-ethynylbenzaldehydes underwent the [4 + 2] benzannulation reactions with numerous alkynes to selectively afford the corresponding naphthalene derivatives in moderate to good yields. Compared with the earlier report [54], two features were established: (1) This reaction is practical and regiospecific; and (2) this reaction was carried out using inexpensive Lewis acid catalyst under additive-free conditions.

Acknowledgments

We thank the National Natural Science Foundation of China (Nos. 20872112 and 20972114), and Zhejiang Provincial Natural Science Foundation of China (No. Y407116) for financial support.

Appendix. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.jorganchem.2010.09.062.

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