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Benzannulation from Alkyne without Metallic Catalysts at Room Temperature to 100 °C

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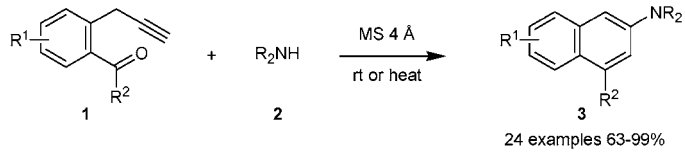
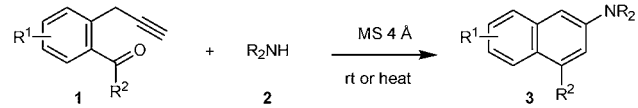
ABSTRACT



An efficient, novel metal-catalyst-free aminobenzannulation of 2-(prop-2-ynyl)(oxo)benzenes 1 with various dialkylamines 2 afforded a variety of 2-aminonaphthalenes 3 in good to excellent yields under mild reaction conditions at room temperature to 100 °C (at most).

Functionalized aromatics and polycyclic aromatics are regarded as useful building blocks in organic synthesis, medicinal chemistry, and materials chemistry. One of the powerful strategies for the construction of these aromatics is acetylene-incorporated aromatic annulation (benzannulation) which was first reported by Berthelot in 1866 through the thermal [2 + 2 + 2] cyclotrimerization of acetylene (400 °C).[1a] Since Reppe[1b] and Vollhardt[1c] developed the transition-metal-catalyzed version of this reaction at relatively lower temperatures, a variety of benzannulation strategies involving Lewis acid- and transition-metal-catalyzed transformations, iodocyclization, and thermal cyclization have been reported.[2] Over the past 10 years, we developed several novel palladium-, gold-, and copper-catalyzed benzannulation reactions.[2b,3] Our goal is to develop an entirely new method for benzannulation with atom-economical and environmentally friendly characteristics.[4] Herein, we report an efficient, unprecedented metallic catalyst-free benzannulation of the 2-(prop-2-ynyl)(oxo)benzenes **1** with dialkylamines **2** under mild reaction conditions, producing various 2-dialkylaminonaphthalenes **3** in good to excellent yields (Scheme 1).

Scheme 1. Synthesis of 2-Aminonaphthalene Derivatives via Aminobenzannulation without Metallic Catalysts



1a: R^1, R^2 = H, H
1b: R^1, R^2 = 4, 5-$(OMe)_2$, H
1c: R^1, R^2 = 5-F, H
1e: R^1, R^2 = H, Me
1f: R^1, R^2 = H, Ph
1g: R^1, R^2 = 4,5-$(OMe)_2$, Me
1h: R^1, R^2 = 5-Cl, Me

Recently, the amine-triggered benzannulation, so-called aminobenzannulation, has been considered an attractive strategy for the construction of the useful amino-substituted

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(3) For reviews, see: (a) Gevorgyan, V.; Yamamoto, Y. *J. Orgnomet. Chem.* **1999**, *576*, 232–247. (b) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817–7831.

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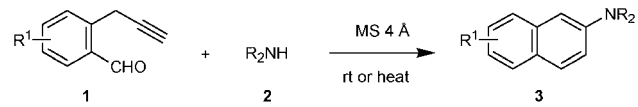
aromatic rings and heterocycles. Since Merlic's group reported an aminobenzannulation method with chromium dienylcarbene,[5] the most common approach involves a transition-metal- or Lewis acid-catalyzed enamine formation/benzannulation reaction of 2-alkynylacetophenones.[6] Würthwein and co-workers developed an interesting aminobenzannulation method based on deprotonation of 2-(1-alkynyl)benzaldimines through a multistep rearrangement cascade.[7] However, these aminobenzannulation methods were limited to the synthesis of 1-aminonaphthalenes. On the other hand, 2-aminonaphthalenes are very important structural frameworks in medicinal chemistry and materials chemistry with a wide range of applications.[8] To our knowledge, the use of aminobenzannulation for the construction of the 2-aminonaphthalenes has been rarely explored.[9]

In the course of the study of the catalytic alkyne−carbonyl metathesis,[10] we uncovered that when 2-(prop-2-ynyl)-benzaldehyde **1a** (0.4 mmol) was treated with diethylamine **2a** as a solvent (2 mL) in the presence of MS 4 Å (200 mg) at ambient temperature for 2 h diethyl-naphthalen-2-yl-amine **3a** was obtained in 93% yield after recovery of the excess amount of diethylamine by distillation followed by a short silica gel chromatography (Table 1, entry 1). The reaction in the absence of MS 4 Å gave **3a** in variable yields of the range of 71−83%. The reaction with the use of 1.5 equiv of Et_2NH and MS 4 Å in the following solvents gave lower yields (40−50%) of **3a**: CH_2Cl_2, CH_3CN, toluene, THF, and MeOH.

The benzannulation of various acyclic and cyclic dialkylamines with 2-(prop-2-ynyl)benzaldehydes **1** is summarized in Table 1. The reaction of the symmetric secondary amines, dimethylamine and dibutylamine, gave the corresponding 2-dialkylaminonaphthalenes **3b** and **3c** in good yields at room temperature (entries 2 and 3). Other acyclic dialkylamines with a 2-methoxyethyl, propargyl, or allyl moiety could be used similarly to give the expected 2-dialkylaminonaphthalenes **3d**−**f** in good yields with prolonged reaction times (entries 4−6). It is noteworthy that methyl-naphthalen-2-yl-prop-2-ynylamine **3e** acts as a rat liver monoamine oxidase inhibitor.[8a] Cyclic

Table 1. Benzannulation of 2-(Prop-2-ynyl)benzaldehydes with Dialkylamines[a]



1 2 3

entry	1	R_2NH (2)	3 (h)	yield (%)[b]
1	**1a**	Et_2NH (**2a**)	**3a** (2)	93
2	**1a**	Me_2NH (**2b**)[c]	**3b** (12)	86
3	**1a**	$(n\text{-Bu})_2NH$ (**2c**)	**3c** (4)	71
4	**1a**	$(Me)(MeOCH_2CH_2)NH$ (**2d**)	**3d** (12)	78
5	**1a**	$(Me)(CHCCH_2)NH$ (**2e**)	**3e** (24)	74
6	**1a**	$(Me)(CH_2CHCH_2)NH$ (**2f**)	**3f** (12)[d]	79
7	**1a**	pyrrolidine (**2g**)	**3g** (2)	84
8	**1a**	piperidine (**2h**)	**3h**(4)[e]	76
9	**1a**	morpholine (**2i**)	**3i** (4)[e]	71
10	**1a**	thiomorpholine (**2j**)	**3j** (24)[f]	83
11	**1a**	*N*-methylpiperazine (**2k**)	**3k** (24)[f]	77
12	**1b**	Et_2NH (**2a**)	**3l** (14)	68
13	**1b**	pyrrolidine (**2g**)	**3m** (5)	93
14	**1c**	Et_2NH (**2a**)	**3n** (5)	86
15	**1c**	pyrrolidine (**2g**)	**3o** (3)	88

[a] General conditions: aldehydes **1** (0.4 mmol), dialkylamine **2** (2 mL, 0.2 M), MS 4 Å (200 mg), at room temperature. The reaction time is shown in parentheses. [b] Isolated yields. [c] A 2.0 M THF solution. [d] 12 h at rt then 1 h at 60 °C. [e] 80 °C. [f] 100 °C.

alkylamines were also suitable for this aminobenzannulation reaction. The reaction of **1a** with pyrrolidine gave the corresponding 1-naphthalen-2-yl-pyrrolidine **3g** in 84% yield under mild reaction conditions (entry 7). Other cyclic amines, such as piperidine, morpholine, thiomorpholine, and *N*-methylpiperazine, were also tolerated, giving the expected 2-aminonaphthalenes **3h**−**k** in good to high yields under the elevated temperatures (entries 8−11).[8b] The 2-(prop-2-ynyl)benzaldehydes substituted with an electron-donating (**1b**) or electron-withdrawing group (**1c**) afforded the desired products, **3l**−**o**, in good to high yields (entries 12−15). A naphthalene derivative (**1d**) reacted with either diethylamine or pyrrolidine at room temperature, producing the corresponding 3-aminophenanthrenes **3p** and **3q** in good yields (Scheme 2). Additional studies

Scheme 2. Formation of 3-Aminophenanthrenes

1d

revealed that, in contrast to the substrates with terminal alkynes or dialkylamines, internal alkynes or less basic amines such as secondary benzylamines and anilines did not undergo the present aminobenzannulation.

Not only the substituted benzaldehydes but also the acetophenone or benzophenone derivatives can be used as

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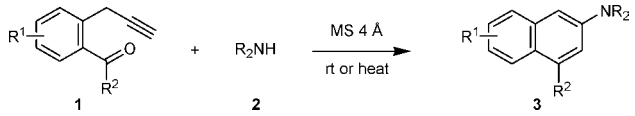
(10) (a) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259–5262. (b) Jin, T.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 3137–3139. (c) Jin, T.; Yang, F.; Liu, C.; Yamamoto, Y. *Chem. Commun.* **2009**, 3533–3535.

substrates for benzannulation. The reaction of **1e**, **1f**, or **1g** with pyrrolidine proceeded smoothly at 80 °C for 12 h, giving the corresponding 2,4-disubstituted 2-aminonaphthalenes **3r**−**t** in high yields (Table 2, entries 1−3). The acetophenones having an electron-withdrawing group (**1h**) on the benzene ring reacted with either diethylamine or pyrrolidine, affording the expected multisubstituted 2-dialkylaminonaphthalenes **3u** and **3v** in good to excellent yields (entries 4 and 5). Interestingly, the acetophenones without substituents (**1e**) or bearing an electron-donating group on the benzene ring (**1g**) reacted with acyclic diethylamine under the same reaction conditions, giving the 1-aminonaphthalenes **4w** and **4x** in high yields instead of forming 2-aminonaphthalenes (Scheme 3).[6] The reason is not clear.

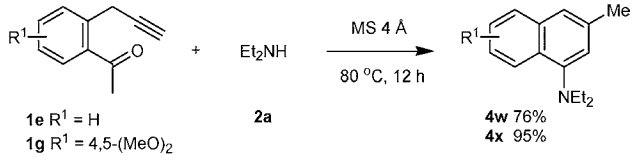
Table 2. Benzannulation of Acetophenone and Benzophenone Derivatives[a]



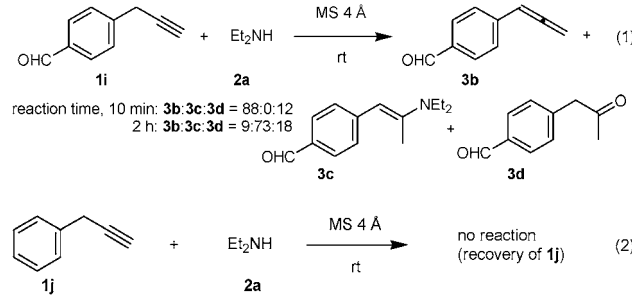
entry	R^1, R^2 (**1**)	R_2NH (**2**)	**3**	yield (%)[b]
1	H, Me (**1e**)	pyrrolidine (**2g**)	**3r**[c]	85
2	H, Ph (**1f**)	pyrrolidine (**2g**)	**3s**	87
3	4,5-$(MeO)_2$, Me (**1g**)	pyrrolidine (**2g**)	**3t**	99
4	5-Cl, Me (**1h**)	Et_2NH (**2a**)	**3u**	78
5	5-Cl, Me (**1h**)	pyrrolidine (**2g**)	**3v**[c]	99

[a] General conditions: ketones **1** (0.4 mmol), dialkylamine **2** (2 mL, 0.2 M), MS 4 Å (200 mg), at 80 °C for 12 h. [b] Isolated yields. [c] Room temperature for 12 h.

Scheme 3. Formation of 1-Aminonaphthalene Derivatives

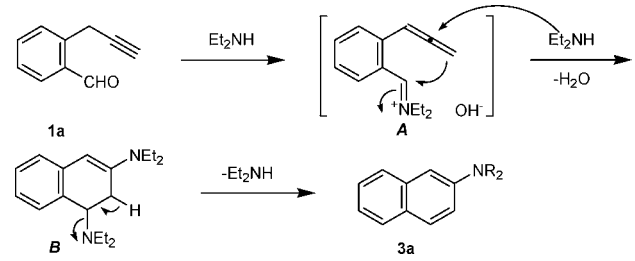


To help clarify the reaction mechanism for the formation of the 2-aminonaphthalenes, we performed the reaction with 4-(prop-2-ynyl)benzaldehyde **1i** and diethylamine at room temperature (eq 1). After 10 min, the allene **3b** was obtained predominantly, while after 2 h the hydroaminated internal enamine **3c** was observed as a major product together with a small amount of the allene **3b** and the hydrolyzed ketone **3d**. When prop-2-ynyl-benzene **1j** was subjected with diethylamine, we never obtained the corresponding allene or enamine product, and **1j** was recovered cleanly (eq 2). These experimental results suggest that the substrate **1i** having an electron-withdrawing group on the benzene ring is readily converted into the corresponding allene. Additionally, in contrast to the previously reported terminal enamine formation/benzannulation stepwise reaction,[6] in the present reaction, the nucleophilic addition of amine to allene and cycloaddition steps should occur simultaneously.



A proposed reaction mechanism is shown in Scheme 4.[11] Initially, rapid isomerization of **1a** in the presence of diethylamine leads to the allene **A**. Subsequent nucleophilic addition of diethylamine to the central carbon of the allene **A** followed by the cycloaddition onto the iminium moiety probably forms the intermediate **B**. Finally, the aromatization of the intermediate **B** through the elimination of amine affords 2-diethylaminonaphthalene **3a**.

Scheme 4. Proposed Reaction Mechanism



In conclusion, we have developed an efficient and general method for the synthesis of 2-dialkylaminonaphthalenes through a novel aminobenzannulation reaction. The reaction proceeds under mild reaction conditions without metal promoters and catalysts. Compared to the previously reported benzannulation protocols, the present approach has an obvious advantage from the viewpoint of atom economy and environmental concern. Further extension of this approach to the synthesis of the biologically important amine-substituted heterocycles and application to materials chemistry are in progress.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) An alternative plausible reaction mechanism for the formation of 2-aminonaphthalenes is a 6-electrocyclization pathway as shown below.