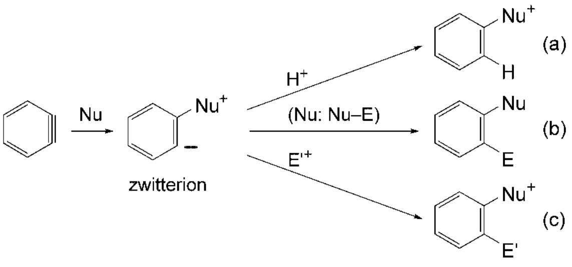
Multicomponent Reactions

Arynes in a Three-Component Coupling Reaction: Straightforward Synthesis of Benzoannulated Iminofurans**

Hiroto Yoshida, Hiroyuki Fukushima, Joji Ohshita, and Atsutaka Kunai**

Arynes are highly strained and kinetically unstable molecules that have been recognized as useful reactive intermediates in organic synthesis.[1] Owing to their low-lying LUMO, arynes exhibit salient electrophilicity, and even neutral nucleophiles, which are inert towards alkynes, readily add to arynes. Hence, considerable attention has been paid to nucleophilic coupling reactions with arynes, and these reactions have been exploited in the construction of complex organic molecules.[2] The coupling reactions proceed through an initially formed zwitterion and can be divided into three categories (Scheme 1): a) formation of a monosubstituted arene by proton abstraction, b) insertion into a nucleophilic–electrophilic σ bond (Nu–E) by intramolecular nucleophilic substitution,[3] and c) three-component coupling by trapping the zwitterion with an electrophile. Although the three-component coupling would be the most attractive approach from a synthetic standpoint for generating molecular complexity and diversity, examples are limited, probably because of the difficulty associated with regulating the reactivity of arynes.[4]



Scheme 1. The reaction of arynes with neutral nucleophiles.

We recently reported novel coupling reactions of arynes with neutral nucleophiles: the synthesis of *N*-alkyl *N'*-aryl imidazolium salts through the addition of imidazoles to arynes (reaction type a, Scheme 1)[5a] and the insertion of arynes into N−CO σ bonds of ureas (reaction type b).[5b,6] Herein we disclose that arynes undergo an unprecedented three-component coupling with isocyanides and aldehydes, thus offering a straightforward method for the synthesis of diverse benzoannulated iminofurans.[7–9]

First, we investigated the reaction of benzyne, generated in situ from 2-(trimethylsilyl)phenyl triflate (**1a**)[10] in the presence of KF and [18]crown-6, with 1,1,3,3-tetramethylbutyl isocyanide (**2a**) and benzaldehyde (**3a**) in THF at 0 °C for 7 h, and observed that the three-component coupling product *N*-(3-phenyl-1(3*H*)-isobenzofuranylidene)-1,1,3,3-tetramethylbutylamine (**4a**) was formed in 65 % yield (Table 1, entry 1).[11] The aromatic aldehydes **3b**, which contains an electron-donating substituent, and **3c**, with an electron-withdrawing substituent, also underwent the reaction efficiently to give the expected products in good yields (Table 1, entries 2 and 3). Furthermore, reactions of the *meta*-substituted aromatic aldehyde **3d** and the sterically congested aldehydes **3e** and **3f** proceeded smoothly to provide the corresponding iminofurans **4d**–**4f** in good yields (Table 1, entries 4–6). The thienyl group in **3g** was compatible with the reaction conditions (Table 1, entry 7),[12] and the aliphatic aldehydes **3h** and **3i** could also be used (Table 1, entries 8 and 9). Besides **2a**, *tert*-butyl (**2b**) and 1-adamantyl isocyanide (**2c**)

---

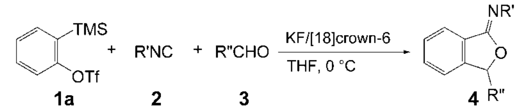
[*] Dr. H. Yoshida, H. Fukushima, Prof. J. Ohshita, Prof. A. Kunai
Department of Applied Chemistry
Graduate School of Engineering, Hiroshima University
Higashi-Hiroshima 739-8527 (Japan)
Fax: (+81) 82-424-5494
E-mail: yhiroto@hiroshima-u.ac.jp
akunai@hiroshima-u.ac.jp

[**] We thank Central Glass Co. Ltd. for a generous gift of trifluoromethanesulfonic anhydride.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200460009

Table 1: Three-component coupling of benzyne, an isocyanide, and an aldehyde.

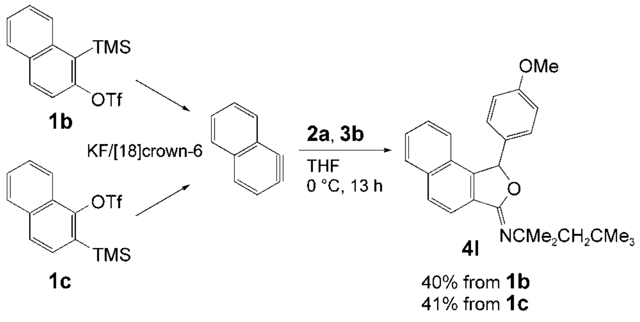


Entry	Isocyanide	R″		*t* [h]	Yield[a] [%]	Product
1	**2a** (R′ = $CMe_2CH_2CMe_3$)	Ph	**3a**	7	65	**4a**
2	**2a**	4-(MeO)C_6H_4	**3b**	7	73	**4b**
3	**2a**	4-(CF_3)C_6H_4	**3c**	7	69	**4c**
4	**2a**	3-(MeO)C_6H_4	**3d**	5	65	**4d**
5	**2a**	2,4-$Me_2C_6H_3$	**3e**	5	61	**4e**
6	**2a**	1-naphthyl	**3f**	5	73	**4f**
7	**2a**	2-thienyl	**3g**	7	50	**4g**
8	**2a**	Et	**3h**	5	50	**4h**
9	**2a**	*t*Bu	**3i**	7	40	**4i**
10	**2b** (R′ = *t*Bu)	1-naphthyl	**3f**	5	49	**4j**
11	**2c** (R′ = 1-Ad)	4-(MeO)C_6H_4	**3b**	24	77	**4k**

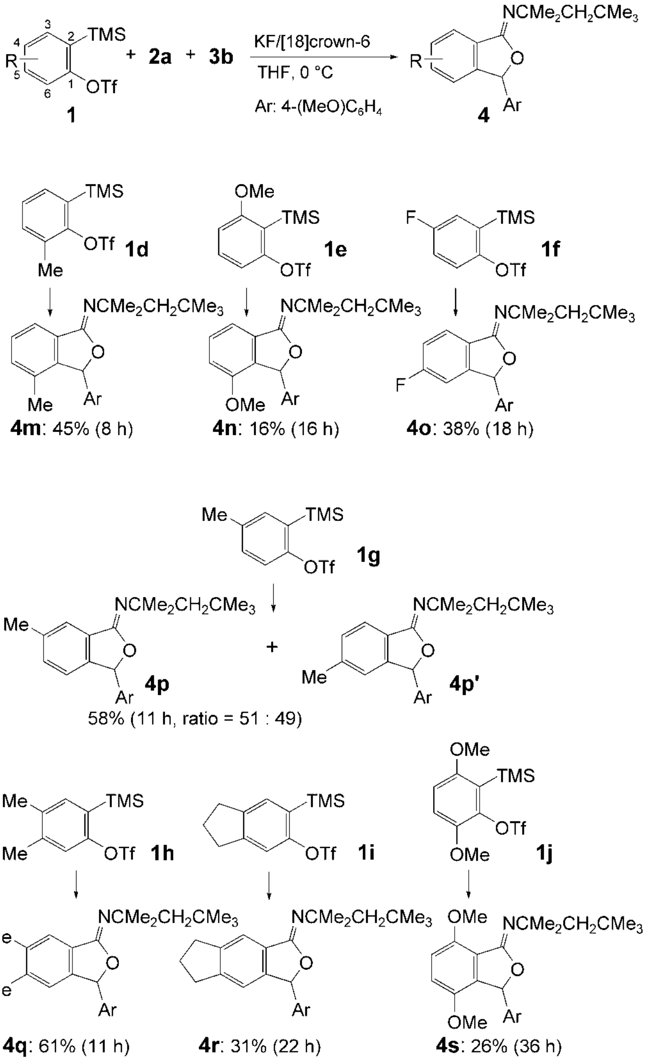
[a] Yield of isolated product based on the isocyanide. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

participated in the reaction to afford the desired product in 49% and 77% yield, respectively (Table 1, entries 10 and 11). In contrast, the reaction of sterically less congested cyclohexyl or *n*-octyl isocyanide resulted in the formation of a complex mixture of products.

As well as unsubstituted benzyne, variously substituted arynes could be used in the reaction. When 1-(trimethylsilyl)-2-naphthyl triflate (**1b**), a 1,2-naphthalyne precursor, was treated with **2a** and **3b**, **4l** was formed as the sole product (Scheme 2). Exclusive formation of **4l** was also observed in the reaction of 2-(trimethylsilyl)-1-naphthyl triflate (**1c**), which confirms the intermediacy of an aryne in the three-component coupling. The reactions of 3-substituted arynes (from **1d** or **1e**) also took place with perfect regioselectivity, whereby the imino moiety was introduced at the sterically less hindered position of the aryne (Scheme 3). The reaction of the aryne derived from **1f**, with a fluoro substituent at position 4, occurred regioselectively to afford **4o** exclusively, whereas the reaction of 4-methylbenzyne (from **1g**) furnished almost equal amounts of the regioisomeric products **4p** and **4p′**. The 4,5-disubstituted arynes derived from **1h** and **1i**, as well as sterically congested 3,6-dimethoxybenzyne (from **1j**), also participated in the reaction to give the corresponding iminofurans **4q**, **4r**, and **4s**.[13]



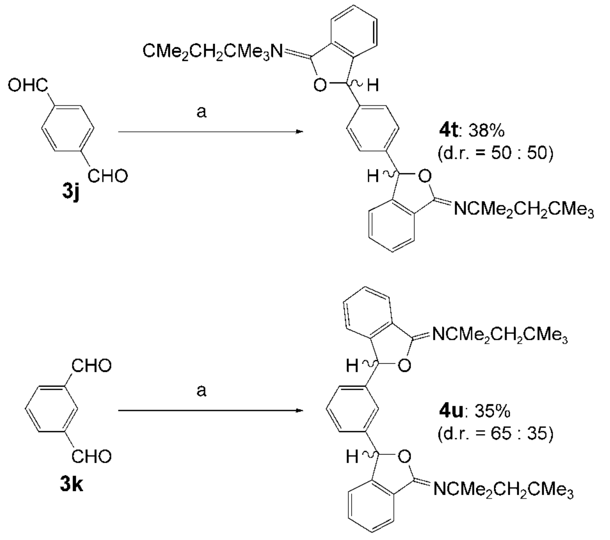
Scheme 2. Three-component coupling of 1,2-naphthalyne, 1,1,3,3-tetramethylbutyl isocyanide, and *p*-anisaldehyde.



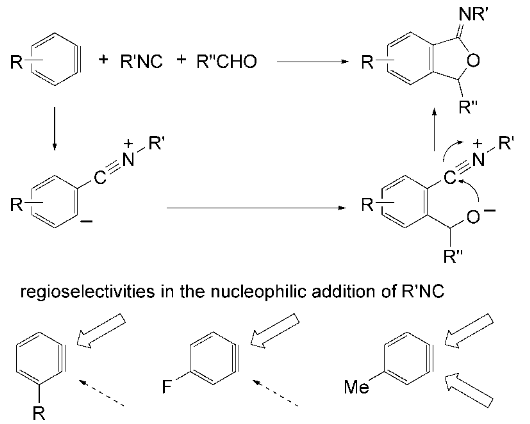
Scheme 3. Three-component coupling with variously substituted arynes.

The reaction was also found to be applicable to an aldehyde with two reactive sites. As depicted in Scheme 4, terephthalaldehyde (**3j**) reacted with benzyne and **2a** to afford **4t** in 38% yield and with a diastereomeric ratio (d.r.) of 50:50. The equivalent reaction of isophthalaldehyde (**3k**) gave the product **4u** with d.r. 65:35.

We propose the nucleophilic attack of the carbon atom of the isocyanide group to the aryne as the initiation step of the three-component coupling (Scheme 5).[14] The resulting zwitterion is then trapped by the aldehyde, and a subsequent intramolecular cyclization affords the product.[15] The observed perfect regioselectivities in the reactions of 1,2-naphthalyne and 3-substituted arynes can be explained rationally as being due to a steric effect, which favors nucleophilic attack at the *meta* position of the substituent.[2a,16] Owing to the strong electron-withdrawing effect of a fluoro substituent, developing negative charge at the *meta*



Scheme 4. Three-component coupling of benzyne, 1,1,3,3-tetramethylbutyl isocyanide, and a phthalaldehyde: a) **1a** (5 equiv), **2a** (2.5 equiv), KF (10 equiv), [18]crown-6 (10 equiv), THF, 0 °C, 7 h.



Scheme 5. Proposed reaction mechanism for the three-component coupling.

position would be stabilized to a greater extent than at the *para* position in the transition state for the addition of an isocyanide to 4-fluorobenzyne, thus resulting in the regioselective formation of **4o**.[17] In contrast, steric and electronic effects around the triple bond would be negligible in the reaction of 4-methylbenzyne, and the isocyanide therefore adds to both ends of the triple bond equally.

In conclusion, we have demonstrated that a variety of arynes, despite their transient nature, can be utilized in a selective three-component coupling reaction with a suitable combination of nucleophile and electrophile. Based upon the present three-component coupling with isocyanides and aldehydes, diverse benzoannulated iminofurans, which are difficult to obtain by conventional methods, can be prepared readily. Further studies on the multicomponent coupling of arynes in the presence of a different combination of reagents are in progress.

Experimental Section

4a: Compound **1a** (0.090 g, 0.30 mmol) was added to a solution in THF (1.0 mL) of KF (0.035 g, 0.60 mmol), [18]crown-6 (0.16 g, 0.60 mmol), **2a** (0.021 g, 0.15 mmol), and **3a** (0.032 g, 0.30 mmol), and the resulting mixture was stirred at 0 °C for 7 h. The reaction mixture was then diluted with ethyl acetate, filtered through a plug of celite, and concentrated. Column chromatography on alumina (eluent: 25 % ethyl acetate/hexane) followed by gel-permeation chromatography (eluent: benzene) gave **4a** as a white powder (0.031 g, 65 %). ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 1.03$ (s, 9 H), 1.47 (s, 6 H), 1.77 (s, 2 H), 6.37 (s, 1 H), 7.13–7.17 (m, 1 H), 7.27–7.41 (m, 7 H), 7.78–7.82 ppm (m, 1 H); ^{13}C NMR (100 MHz, [D$_8$]THF): $\delta =$ 30.9, 32.4, 32.7, 56.2, 57.9, 85.6, 122.9, 124.2, 127.4, 129.2, 129.5, 129.7, 131.8, 133.0, 140.7, 147.1, 152.5 ppm; HRMS calcd for $C_{22}H_{27}NO$ (M^+): 321.2093; found: m/z 321.2100.

Received: March 16, 2004 [Z460009]

Keywords: arynes · isocyanides · multicomponent reactions · oxygen heterocycles · regioselectivity

---

[1] For reviews, see: a) R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York, **1967**; b) H. Hart in *The Chemistry of Triple-Bonded Functional Groups, Supplement C2* (Ed.: S. Patai), Wiley, Chichester, **1994**, chap. 18; c) H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701.

[2] a) S. V. Kessar in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 483–515; b) E. R. Biehl, S. P. Khanapure, *Acc. Chem. Res.* **1989**, *22*, 275.

[3] For Te–Te, see: a) N. Petragnani, V. G. Toscano, *Chem. Ber.* **1970**, *103*, 1652; for S–S, see: b) J. Nakayama, T. Tajiri, M. Hoshino, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2907; for C–Si, see: c) Y. Sato, Y. Kobayashi, M. Sugiura, H. Shirai, *J. Org. Chem.* **1978**, *43*, 199.

[4] Three-component coupling reactions of arynes have been carried out previously with anionic nucleophiles: a) A. I. Meyers, P. D. Pansegrau, *Tetrahedron Lett.* **1983**, *24*, 4935; b) A. I. Meyers, P. D. Pansegrau, *J. Chem. Soc. Chem. Commun.* **1985**, 690; c) S. Tripathy, R. LeBlanc, T. Durst, *Org. Lett.* **1999**, *1*, 1973.

[5] a) H. Yoshida, S. Sugiura, A. Kunai, *Org. Lett.* **2002**, *4*, 2767; b) H. Yoshida, E. Shirakawa, Y. Honda, T. Hiyama, *Angew. Chem.* **2002**, *114*, 3381; *Angew. Chem. Int. Ed.* **2002**, *41*, 3247.

[6] We also reported palladium-catalyzed insertion reactions of arynes into element–element σ bonds; for carbostannylation (C–Sn), see: a) H. Yoshida, Y. Honda, E. Shirakawa, T. Hiyama, *Chem. Commun.* **2001**, 1880; for bissilylation (Si–Si), see: b) H. Yoshida, J. Ikadai, M. Shudo, J. Ohshita, A. Kunai, *J. Am. Chem. Soc.* **2003**, *125*, 6638.

[7] For previous reports on the synthesis of benzoannulated iminofurans, see: a) A. I. Meyers, M. A. Hanagan, L. M. Trefonas, R. J. Baker, *Tetrahedron* **1983**, *39*, 1991; b) W. Meise, B. Suedkamp, *Arch. Pharm.* **1987**, *320*, 1210.

[8] For the Lewis acid mediated synthesis of iminofurans with isocyanides, see: a) Y. Ito, H. Kato, T. Saegusa, *J. Org. Chem.* **1982**, *47*, 741; b) N. Chatani, M. Oshita, M. Tobisu, Y. Ishii, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 7812.

[9] For the three-component coupling of alkynes, isocyanides, and aldehydes to give 2-aminofuran derivatives, see: a) V. Nair, A. U. Vinod, *Chem. Commun.* **2000**, 1019; b) A. Fayol, J. Zhu, *Angew. Chem.* **2002**, *114*, 3785; *Angew. Chem. Int. Ed.* **2002**, *41*, 3633; c) A. Fayol, J. Zhu, *Org. Lett.* **2004**, *6*, 115.

[10] Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211.

[11] Although structural elucidation of the product of the three-component coupling by NMR spectroscopy showed it to be a

single isomer, we could not determine the exact stereochemistry (*E* or *Z*) of the imine unit.

[12] For the Diels–Alder reaction of thiophene with an aryne, see: D. D. Callander, P. L. Coe, J. C. Tatlow, *J. Chem. Soc. Chem. Commun.* **1966**, 143.

[13] Owing to the complexity of the reaction mixtures, we did not pursue the identification of by-products of low-yielding reactions. At present, the reasons for which the desired products formed in low yields in the reactions of **1e**, **1i**, and **1j** are unclear.

[14] R. Knorr, *Chem. Ber.* **1965**, *98*, 4038.

[15] A referee suggested another mechanism, in which the isocyanide acts as an electrophile: Nucleophilic attack of the oxygen atom of the carbonyl group of the aldehyde at the carbon atom of the isocyanide group produces a 1,3-dipole, which then undergoes 1,3-dipolar cycloaddition with an aryne to afford the product. Although this alternative mechanism can not be ruled out entirely, the mechanism proposed by us appears more likely, as the electrophilic coupling of an isocyanide with a neutral nucleophile is generally known to be sluggish, except in special cases. Furthermore, if the oxygen atom of the carbonyl group acted as a nucleophile, it would first interact with the highly electrophilic aryne, rather than the isocyanide, to provide a different product to those described herein. For the electrophilic coupling of an isocyanide with a neutral nucleophile, see: a) M. Suginome, T. Fukuda, Y. Ito, *Org. Lett.* **1999**, *1*, 1977; for the nucleophilic coupling of a carbonyl compound with an aryne, see: b) H. Heaney, C. T. McCarty, *J. Chem. Soc. Chem. Commun.* **1970**, 123.

[16] Because of the electron-donating nature of the methyl substituent, the regioselectivity of the reaction of 3-methylbenzyne seems to be unfavorable electronically. However, such regioselectivity is often observed in nucleophilic coupling reactions with 3-methylbenzyne; see: T. K. Vinod, H. Hart, *Tetrahedron Lett.* **1988**, *29*, 885.

[17] Similar regioselectivity was observed in nucleophilic coupling reactions with 4-chlorobenzyne: a) J. F. Bunnett, C. Pyun, *J. Org. Chem.* **1969**, *34*, 2035; b) J. F. Bunnett, J. K. Kim, *J. Am. Chem. Soc.* **1973**, *95*, 2254.