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DIHALOGENATIVE CYCLIZATION FOR THE SYNTHESIS OF 4-BROMO-1-BROMOALKYL-5-ARYL/ALKYL/ALKENYL−PYRAZOLES

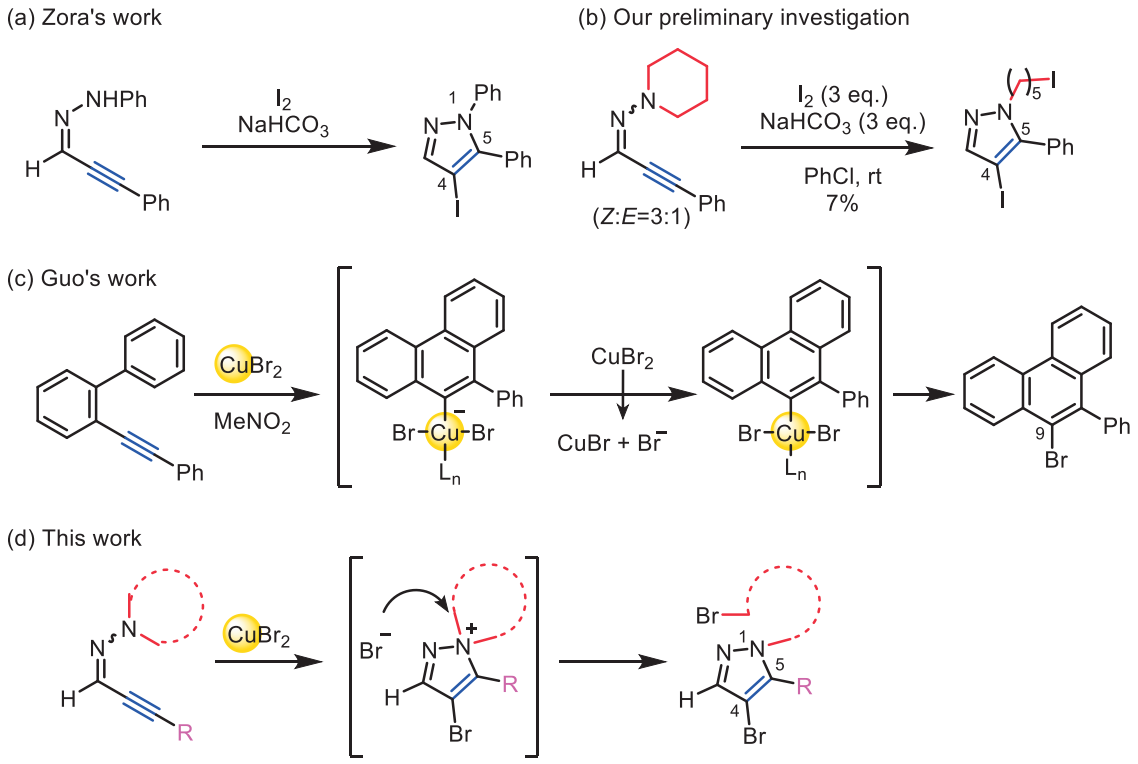
Motohiro Yasui, Maki Hasegawa, Keiji Konishi, Norihiko Takeda, and Masafumi Ueda*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan, E-mail: masa-u@kobepharma-u.ac.jp

Abstract – A copper-mediated domino reaction involving cyclization, bromination, and nucleophilic substitution of *N*,*N*-disubstituted hydrazones, which are labile under oxidative conditions, to synthesize 4-bromo-1-bromoalkyl-5-aryl/alkyl/alkenyl-pyrazoles, is achieved. This method features the simultaneous construction of pyrazoles and two C-Br bonds, which are synthetically useful.

Pyrazole is an important skeletal compound of various pharmaceuticals,[1] pesticides,[2] synthetic reagents,[3] and chemical materials.[4] Therefore, the synthetic method of pyrazoles has long been an attractive research topic. Classically, pyrazoles are synthesized by cyclocondensation of 1,3-carbonyl derivatives or by a 1,3-dipolar cycloaddition reaction. However, these methods often have low regioselectivity and a limited substrate scope. Therefore, novel methods have been developed to overcome these problems in recent years.[1d,5] The cyclization of alkynylhydrazones is a valuable method for the direct and selective synthesis of 1,4,5-substituted pyrazoles, which have substituents in sterically hindered positions. The reaction proceeds through electrophilic cyclization of *N*-monosubstituted alkynylhydrazones, followed by protonation,[6] iodination,[7] fluorination,[8] trifluoromethylation,[9] chalcogenylation,[10] or borylation (Scheme 1a).[11] In contrast, as a reaction of *N*,*N*-disubstituted hydrazones,[12] which are labile under oxidative conditions, only a copper-catalyzed rearrangement reaction has been reported,[13] and not electrophilic cyclization. Indeed, our preliminary investigation based on the conditions of Zora *et al*,[7] showed that the reaction of alkynylhydrazone using iodine was complicated to afford iodocyclization product in a poor yield (Scheme 1b). Therefore, we devised a novel strategy for the synthesis of halogenated pyrazoles using *N*,*N*-disubstituted hydrazones.

Halogens are employed for various chemical transformations, and are therefore a universal building block in organic synthetic chemistry.[14] In addition, halogens are components of various natural products,[15] pharmaceuticals,[16] and pesticides.[17] Therefore, efficient construction methods for carbon-halogen bonds have remained a focus of research and been developed.[18] In recent years, halogenation[19] and arylation[20,21] *via* single electron transfer (SET) of CuX_2 (X = Cl, Br or I) have been developed. For example, Guo *et al.* reported halocyclization of arene-alkyne with $CuBr_2$ to afford 9-bromophenanthrenes (Scheme 1c).[19a] As SET of $CuBr_2$ generates a nucleophilic bromide ion *in situ*, we expected a domino reaction of *N*,*N*-disubstituted hydrazones with $CuBr_2$ involving sequential intramolecular nucleophilic addition, halogenation, and nucleophilic substitution proceeded to obtain 4-bromo-1-bromoalkyl-5-substituted pyrazoles (Scheme 1d).

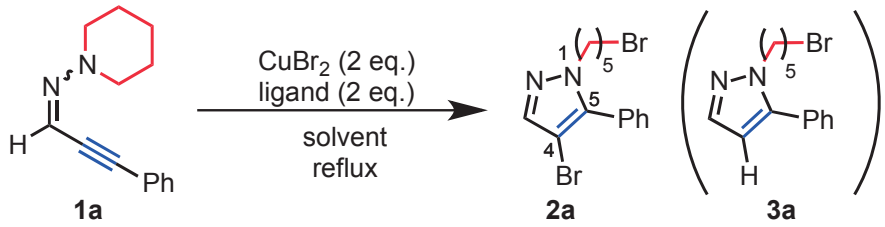


Scheme 1. Halocyclization of alkyne

To realize the dihalogenative cyclization, we optimized the reaction conditions. First, *N*-piperidyl-hydrazone **1a** was treated with two equivalents of $CuBr_2$ in nitromethane under reflux to afford 4-bromo-1-bromopentyl-5-phenylpyrazole **2a** in 16% yield and 4-protonated pyrazole **3a** in 20% yield (Table 1, entry 1).[19a] The structure of **2a** was determined by analysis of the spectroscopic data, including 2D-NMR (COSY, HSQC, HMBC, and NOESY), and comparison with a previous report.[22] Next, various ligands were investigated because we assumed that they would have a significant effect on the domino

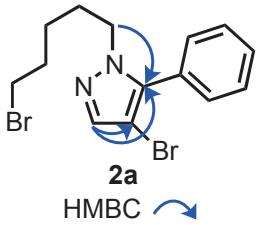
reaction. Pyridine, tetramethylethylenediamine (TMEDA), 2,2-bipiridyl, and 2,2':6'2"-terpyridine were employed in chlorobenzene under reflux, but decreased the yields (entries 2-5). Meanwhile, 2,2'-bis(2-oxazoline) and neocuproine accelerated the domino reaction to give **2a** in 42 and 37% yields, respectively (entries 6 and 7). Finally, an investigation of substituents on the phenanthroline skeleton was conducted. The yield of **2a** was up to 55% when bathocuproine was employed (entries 8 and 9).

Table 1. Investigation of ligands



1a (*Z*:*E*=3:1) **2a** **3a**

entry	ligand	solvent	yield (%)
1[a)]	-	$MeNO_2$	16 (**3a**: 20)
2	pyridine[b)]	PhCl	8
3	TMEDA	PhCl	-
4	2,2-bipyridyl	PhCl	6
5	2,2':6',2"-terpyridine	PhCl	4
6	2,2'-bis(2-oxazoline)	PhCl	42
7	neocuproine	PhCl	37
8	bathophenanthroline	PhCl	26
9	bathocuproine	PhCl	55

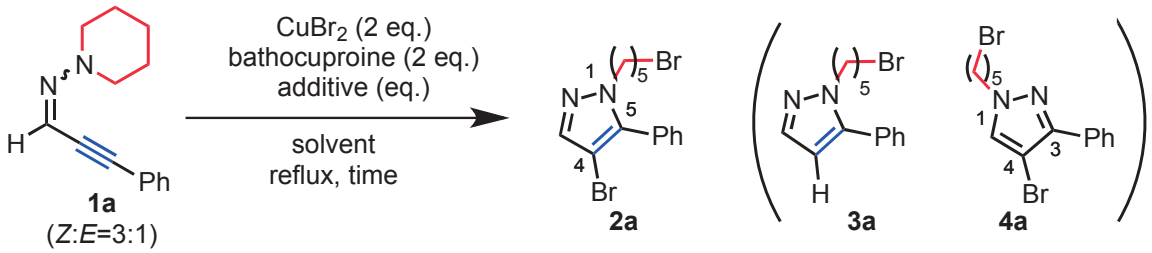


2a
HMBC

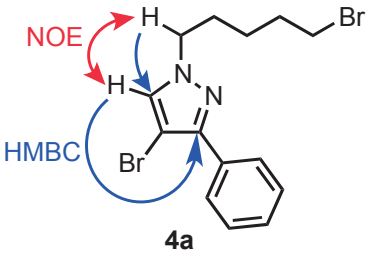
a) K_3PO_4 (0.5 eq.) was added as an additive.
b) 10 equivalents of pyridine was used.

To further improve yields, solvents, temperature, and additives were investigated. The investigation of aprotic polar solvent, such as DMF, 1,4-dioxane, and nitromethane, under heating condition did not increase the yield of **2a** as compared with chlorobenzene (Table 2, entries 1-4). As expected, a significant amount of protonated by-product **3a** was obtained with ethanol, which is a protic solvent (entry 5). In addition, small amount of (*E*)-**1a** was recovered when one equivalent of copper species was used (entry 6). As protonation not only occurred in entry 5, but **3a** was detected in the other conditions, proton scavengers were further investigated. The addition of molecular sieve 4A (MS4A) suppressed the generation of **3a**, but accelerated the generation of **4a** (entry 7). In contrast, the yield of **2a** was increased by up to 71% when K_3PO_4 was employed (entry 8). Finally, 4-bromo-1-bromopentyl-3-phenylpyrazole **4a**, which would be generated by sequential nucleophilic substitution,[23,24] was obtained when the reaction time was prolonged to 64 h (entry 9).

Table 2. Investigation of solvents and additives

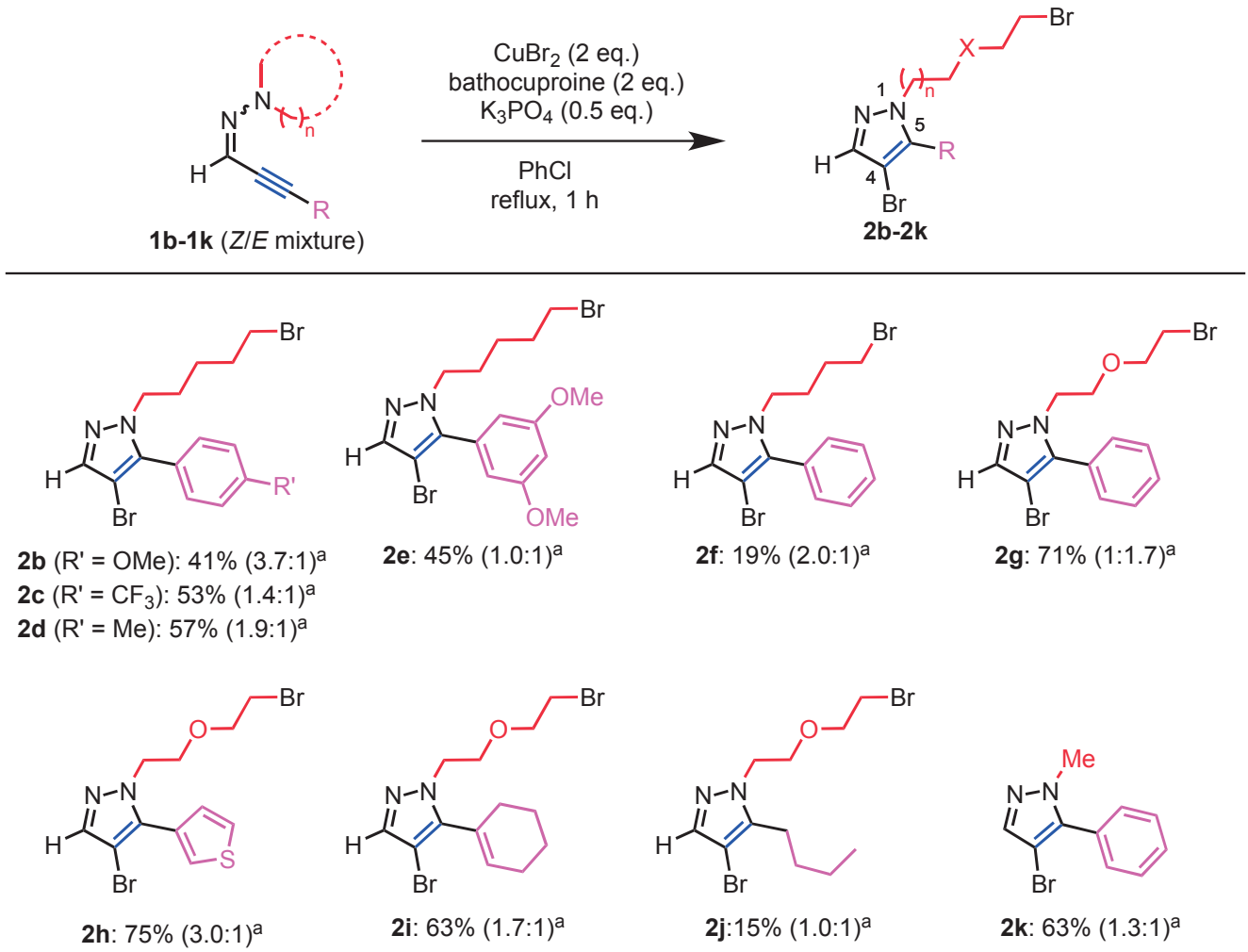


entry	additive (eq.)	solvent	time (h)	yield (%)
1	-	PhCl	1	55
2	-	DMF[a)]	1	15
3	-	1,4-dioxane	1	41
4	-	$MeNO_2$	1	26
5	-	EtOH	1	25 (**3a**: 16)
6[a)]	-	PhCl	1	37 ((*E*)-**1a**: 7)
7	MS4A (180 mg/mL)	PhCl	1	23 (**4a**: 18)
8	K_3PO_4 (0.5)	PhCl	1	71
9	K_3PO_4 (0.5)	PhCl	64	0 (**4a**: 75)



a) The reaction was carried out at 135 °C
b) $CuBr_2$ (1 eq.) and bathocuproine (1 eq.) were used.

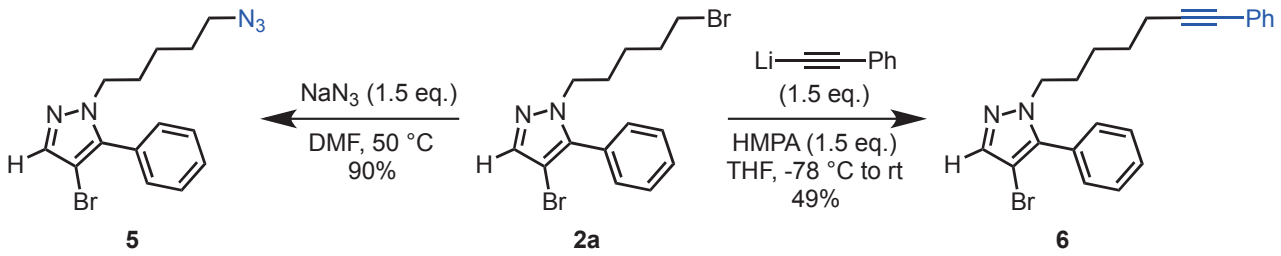
With the optimized conditions determined, the substrate scope was investigated. First, to confirm substituent effects, substituents at the 4-position on the benzene-ring linked to alkyne terminus were investigated. Both electron-donating as well as withdrawing groups resulted in moderate yields of 4-bromo-1-bromopentylpyrroles **2b**–**2e** (Scheme 2). The cyclization of *N*-pyrrolidino hydrazone **1f** was sluggish and produced 4-bromo-1-bromobutyl-5-phenylpyrazole **2f** in poor yield, whereas the reaction of *N*-morpholino hydrazone **1g** proceeded smoothly to afford the corresponding bromopyrazole **2g** in 71% yield. These results suggest that the efficiency of bromocyclization is dependent on the cyclic amine moiety rather than the ratio of the *E*/*Z* isomer. The alkynyl hydrazone **1h**, bearing a thiophene on an alkyne terminus, was able to give **2h** in 75% yield. In addition, 5-alkenylpyrazole **2i** was obtained in good yield (63%) as well as 5-alkyl pyrazole **2j**, albeit in low yield (15%). Finally, the use of *N*,*N*-dimethyl hydrazone **1k** afforded 4-bromo-5-phenyl-1-methylpyrazole **2k** in 63% yield.



a) In parentheses is the ratio of *Z* to *E* of the starting material.

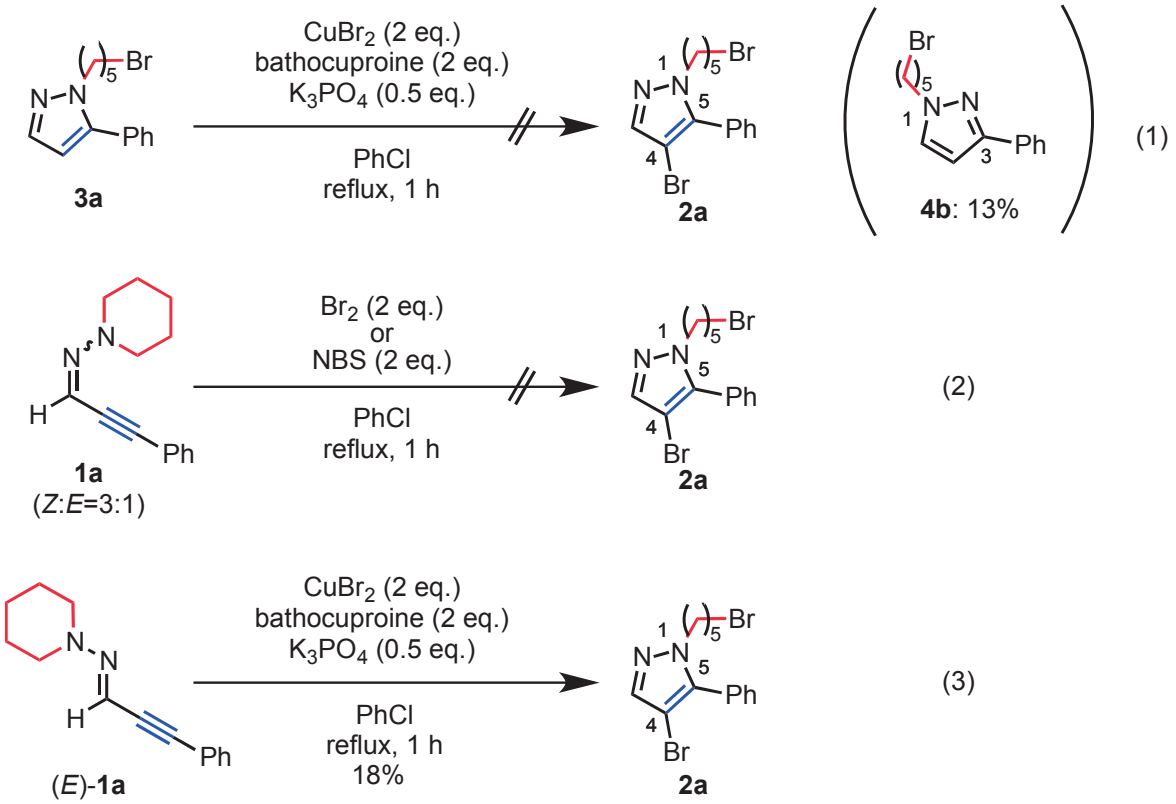
Scheme 2. Scope of dihalogenative cyclization[a]

To demonstrate the synthetic utility of our methodology, further chemical transformations of **2a** were performed (Scheme 3). First, bromopyrazole **2a** was treated with NaN_3 in DMF at 50 °C to afford the corresponding alkyl azide **5** in 90% yield. In addition, alkynylation of **2a** proceeded to give alkyne **6** in 49% yield.



Scheme 3. Transformation of **2a**

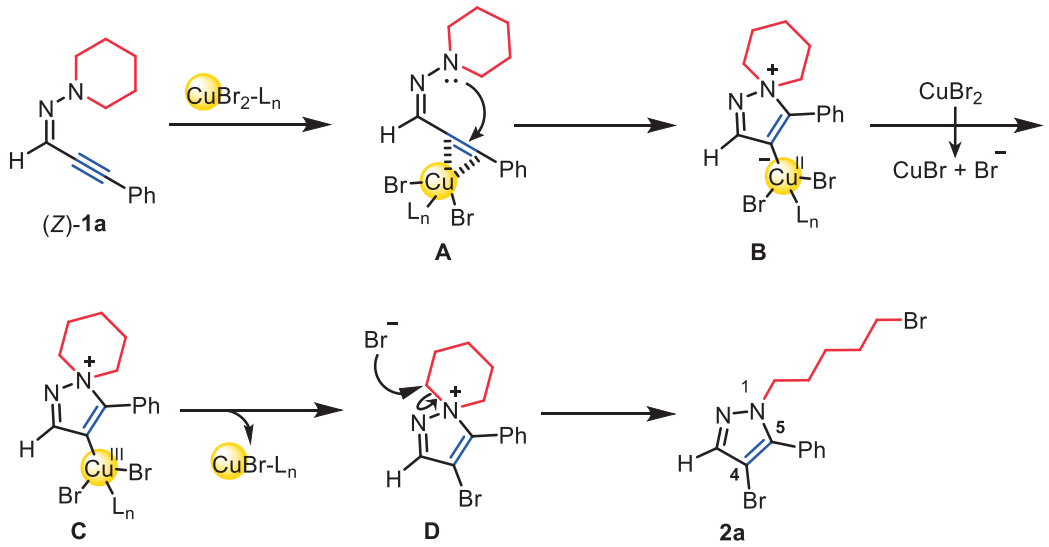
To clarify the details of the reaction, some control experiments were conducted. First, 4-bromopyrazole **2a** was not detected at all, however, **4b** was obtained when protonated pyrazole **3a** was treated under the optimized conditions (Scheme 4, eq. 1). This indicated that **2a** was not generated from **3a** as a reaction



Scheme 4. Control experiments

intermediate. The use of bromine and NBS, which are electrophilic brominating reagents, resulted in a complex mixture, not **2a** (Eq. 2). Therefore, $CuBr_2$ was found to be appropriate for the domino reaction. Finally, when a single isomer of (*E*)-**1a** was employed, **2a** was obtained at 18% yield (Eq. 3). The result suggests that the reaction rate of the (*E*)-isomer is slower, probably because the (*E*)-isomer requires isomerization to (*Z*)-isomer.[25]

The proposed mechanism of the copper-mediated domino dibromonative cyclization is shown in Scheme 5. First, the alkyne moiety of hydrazone (*Z*)-**1a** coordinates to $CuBr_2$ to generate copper complex **A** and activates the alkyne moiety. Subsequently, 5-*endo-dig* cyclization proceeds to form vinyl copper(II) intermediate **B**. Another $CuBr_2$ undergoes SET to give vinyl copper(III) species **C** along with CuBr and a bromide ion. Reductive elimination of intermediate **C** affords vinyl bromide **D**.[19] Finally, the bromide ion, which is generated *in situ*, reacts with **D** to give 4-bromo-1-bromoalkyl-5-substituted pyrazole **2a**.



Scheme 5. Proposed reaction mechanism

In summary, we have developed copper-mediated dibromonative cyclization for the synthesis of 4-bromo-1-alkylbromo-5-aryl/alkyl/alkenyl-pyrazoles. This method enables the synthesis of halogenated pyrazoles using *N*,*N*-disubstituted hydrazones, which is difficult to carry out with electrophilic halogenating reagents such as Br_2 and NBS. In addition, the simultaneous introduction of two C-Br bonds, which would be synthetically useful, is featured in the domino reaction.

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SUPPORTING INFORMATION

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26926/103/.

REFERENCES AND NOTES

1. (a) J. J. Li, 'Heterocyclic Chemistry in Drug Discovery', Chapter 5, John-Wiley & Sons, Inc., Hoboken, New Jersey, 2013, pp. 198-230; (b) M. F. Khan, M. M. Alam, G. Verma, W. Akhtar, M. Akhter, and M. Shaquiquzzaman, *Eur. J. Med. Chem.*, 2016, **120**, 170; (c) A. Ansari, A. Ali, M. Asif, and Shamsuzzaman, *New J. Chem.*, 2017, **41**, 16; (d) K. Karrouch, S. Radi, Y. Ramli, J. Taoufik, Y.

N. Mabkhot, F. A. A.-aizari, and M. Ansar, *Molecules*, 2018, **23**, 134; (e) Ş, Küçükgüzel and S. Şenkardeş, *Eur. J. Med. Chem.*, 2015, **97**, 786.

2. (a) G. P. Lahm, D. Cordova, and J. D. Barry, *Bioorg. Med. Chem.*, 2009, **17**, 4127; (b) G. P. Lahm, T. M. Stevenson, T. P. Selby, J. H. Freudenberge, D. Cordova, L. Flexner, C. A. Bellin, C. M. Dubas, B. K. Smith, K. A. Hughes, J. G. Hollingshaus, C. E. Clark, and E. A. Benner, *Bioorg. Med. Chem.*, *Lett.*, 2007, **17**, 6274.
3. (a) R. A. Singer, M. Doré, J. E. Siese, and M. A. Berliner, *Tetrahedron Lett.*, 2006, **47**, 3727; (b) R. A. Singer, S. Caron, R. E. McDermott, P. Arpin, and N. M. Do, *Synthesis*, 2003, 1727; (c) S. Takizawa, Y. Honda, M. A. Arai, T. Kato, and H. Sasai, *Heterocycles*, 2003, **60**, 2551; (d) M. V.-Chumillas, S. Tanase, L. Jos. de. Jongh, and J. Reedijk, *Eur. J. Inorg. Chem.*, 2010, 3403.
4. (a) E. Cavero, S. Uriel, P. Romero, J. L. Serrano, and R. Giménez, *J. Am. Chem. Soc.*, 2007, **129**, 11608; (b) J. Barberá, A. Elduque, R. Giménez, L. A. Oro, and J. L. Serrano, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2832; (c) Y. Zhang, D. A. Parrish, and J. M. Shreeve, *Chem. Eur. J.*, 2012, **18**, 987; (d) P. Yin, D. A. Parrish, and J. M. Shreeve, *J. Am. Chem. Soc.*, 2015, **137**, 4778; (e) C. Lei, H. Yang, and G. Cheng, *Dalton Trans.*, 2020, **49**, 1660.
5. (a) R. R. Gupta, M. Kumar, and V. Gupta, 'Heterocyclic Chemistry', Vol. II, Springer-Verlag, Berlin, 1999, pp. 435-455; (b) T. Eicher, S. Hauptmann, and A. Speicher, 'The Chemistry of Heterocycles Structures, Reactions, Synthesis, and Applications Third, Completely Revised and Enlarged Edition', Wiley-VCH Verlag & Co. KGaA, Weinheim, 2012, pp. 236-243.
6. M. Zora and A. Kivrak, *J. Org. Chem.*, 2011, **76**, 9379.
7. M. Zora, A. Kivrak, and C. Yazici, *J. Org. Chem*., 2011, **76**, 6726.
8. J. Qian, Y. Liu, J. Zhu, B. Jiang, and Z. Xu, *Org. Lett.*, 2011, **13**, 4220.
9. (a) Q. Qang, L. He, K. K. Li, and G. C. Tsui, *Org. Lett.*, 2017, **19**, 658; (b) G, Ji, X, Wang, S. Zhang, Y. Xu, Y. Ye, M. Li, Y. Zhang, and J. Wang, *Chem. Commun.*, 2014, **50**, 4361.
10. X. Yu, Y.-Z. Shang, Y.-F. Cheng, J. Tian, Y. Niu, and W.-C. Gao, *Org. Biomol. Chem.*, 2020, **18**, 1806.
11. K. N. Tu, S. Kim, and S. A. Blum, *Org. Lett.*, 2019, **21**, 1283.
12. (a) L. Liu, L. Du, D. Z.-Negrerie, and Y. Du, *RSC Adv.*, 2015, **5**, 29774; (b) H. G. Stenmark, A. Brazzale, and Z. Ma, *J. Org. Chem.*, 2000, **65**, 3875; (c) E. J. Grayson and B. G. Davis, *Org. Lett.*, 2005, **7**, 2361.
13. I. Nakamura, N. Shiraiwa, R. Kanazawa, and M. Terada, *Org. Lett.*, 2010, **12**, 4198.
14. R. Xavi, 'C-H and C-X bond functionalization: transition metal mediation', RSC Publishing, Cambridge, 2013, pp. 114-118.
15. (a) C. Wagner, M. E. Omari, and G. M. König, *J. Nat. Prod.*, 2009, **72**, 540; (b) P. M. Pauletti, L. S.

Comtra, C. G. Braguine, A. A. da A. Filho, M. L. A. de Silva, W. R. Cunha, and A. H. Januário. *Mar. Drugs*, 2010, **8**, 1526; (c) K. Benkendorff, *Mar. Drugs*, 2013, **11**, 1370; (d) D. R. Smith, S. Grüschow, and R. J. Goss, *Curr. Opin. Chem. Biol.*, 2013, **17**, 276; (e) C. S. Neumann, D. G. Fujimori, and C. T. Walsh, *Chem. Biol*., 2008, **15**, 99.

16. (a) J. Wang, M. S.-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (b) A. Jain, L. S. Duvvuri, S. Farah, N. Beyth, A. J. Damb, and W. Khan, *Adv*. *Healthcare Mater*., 2014, **3**, 1969; (c) C. Kim and Y.-N. Cha, *Amino Acids*, 2014, **46**, 89; (d) J.-P. Bégué and D. Bonnet-Delpon, *J. Fluorine. Chem.*, 2006, **127**, 992; (e) A. S. Christophersen, *Toxicol. Lett.*, 2000, **112**, 127.
17. (a) P. Jeschke, *Pest. Manag. Sci.*, 2010, **66**, 10; (b) T. Fujiwara and D. O'Hagan, *J. Fluorine. Chem.*, 2014, **167**, 16.
18. A. Vigalok, 'Topics in Organometallic Chemistry C-X bond Formation', Vol. 31, Springer, Verlag, Berlin, 2010, pp. 1-38.
19. (a) W. Liu, J. Chen, R. Jin, D. Xu, Y. Li, F. Ba, G. Gu, Y. Kuang, and H. Guo, *Org. Chem. Front.*, 2016, **3**, 852; (b) B. Yao, D.-X. Wang, Z.-T. Huang, and M.-X. Wang, *Chem. Commun.*, 2009, 2899; (c) A. Castas, M. Canta, M. Solá, M. Costas, and X. Ribas, *J. Am. Chem. Soc.*, 2011, **133**, 19386; (d) B. Yao, Z.-L. Wang, H. Zhang, D.-X. Wang, L. Zhao, and M.-X. Wang, *J. Org. Chem.*, 2012, **77**, 3336; (e) N. Xin and S. Ma, *Eur. J. Org. Chem.*, 2012, 3806; (f) J. Xiang, R. Yuan, R. Wang, N. Yi, L. Lu, H. Zou, and H. He, *J. Org. Chem.*, 2014, **79**, 11378.
20. S. D. McCann and S. S. Stahl, *Acc. Chem. Res.*, 2015, **48**, 1756.
21. A. E. King, B. L. Ryland, T. C. Brunold, and S. S. Stahl, *Organometallics*, 2012, **31**, 7948.
22. K. Kano, D. Scarretti, J. C. Warner, and J.-P. Anselme, *Can. J. Chem.*, 1986, **64**, 2211.
23. (a) M. Ye, A. J. F. Edmunds, J. A. Morris, D. Sale, Y. Zhang, and J.-Q. Yu, *Chem. Sci.*, 2013, **4**, 2374; (b) E. L. Elliott, S. M. Bushell, M. Cavero, B. Tolan, and T. R. Kelly, *Org. Lett.*, 2005, **7**, 2449; (c) K. Inamoto, M. Katsuno, T. Yoshino, Y. Arai, K. Hiroya, and T. Sakamoto, *Tetrahedron*, 2007, **63**, 2695; (d) J. Yang and P. Gharagozloo, *Synth. Commun.*, 2005, **35**, 409.
24. (a) N. Guiliol, B. Martin, Z. Janousek, and H. G. Viehe, *Synth. Commun.*, 1989, **19**, 2825; (b) L. Strekowski, J. Zhang, J. Sączewski, and E. Wolińska, *Aust. J. Chem.*, 2014, **68**, 196.
25. Preliminary DFT calculation using Spartan'18 (Wavefunction, Inc., Irvine, CA) of the activation energy during isomerization from (*E*) to (*Z*) isomer was conducted, see Supporting Information.