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Consecutive Gold(I)-Catalyzed Cyclization Reactions of *o*-(Buta-1,3-diyn-1-yl-)-Substituted *N*-Aryl Ureas: A One-Pot Synthesis of Pyrimido[1,6-*a*]indol-1(2*H*)-ones and Related Systems

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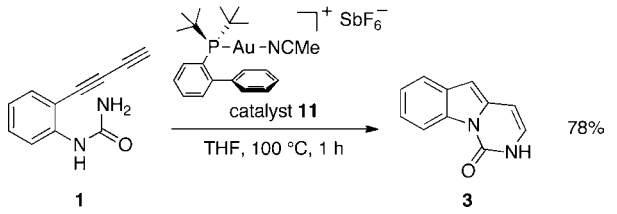
ABSTRACT



Treatment of readily available *o*-(buta-1,3-diyn-1-yl-)-substituted *N*-aryl ureas such as 1 with the Au(I)-catalyst 11 affords, via a twofold cyclization process, the isomeric pyrimido[1,6-*a*]indol-1(2*H*)-one 3 in good yield.

o-Alkynylanilines and certain related systems readily cyclize under various conditions to give the corresponding indoles, and these types of processes have found extensive application in the synthesis of a wide range of biologically relevant systems.[1−3] Surprisingly, and despite the prospects they offer for rapidly assembling polyfused heteroaromatic systems, extensions of this type of process to substrates incorporating *ortho*-related diynes and bis-heteroatom-based nucleophiles do not appear to have been investigated.[4] The prototypical process we envisaged is shown in Figure 1 and involves the conversion of the monocyclic *o*-disubstituted arene **1** or **2** into their tricyclic and thermodynamically more stable isomer **3** or **4**, respectively.[5] Herein we report the successful implementation

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(1) See, for example: (a) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571 and references cited therein. (b) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (c) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610. (d) Kamijo, S.; Sasaki, Y.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 35. (e) Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F. *Adv. Synth. Catal.* **2010**, *352*, 971. (f) Alsabeh, P. G.; Lundgren, R. J.; Longobardi, L. E.; Stradiotto, M. *Chem. Commun.* **2011**, *47*, 6936. (g) Wang, H.; Li, Y.; Jiang, L.; Zhang, R.; Jin, K.; Zhao, D.; Duan, C. *Org. Biomol. Chem.* **2011**, *9*, 4983. (h) Hirano, K.; Inaba, Y.; Takasu, K.; Oishi, S.; Takemoto, Y.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 9068. (i) Chen, C.-C.; Yang, S.-C.; Wu, M.-J. *J. Org. Chem.* **2011**, *76*, 10269. (j) Wetzel, A.; Gagosz, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7354.

(2) "Double-barrelled" versions of such processes leading to 2,2′-biindolyls are known: (a) Shin, K.; Ogasawara, K. *Synlett* **1995**, 859. (b) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841. (c) Abbiati, G.; Arcadi, A.; Beccalli, E.; Bianchi, G.; Marinelli, F.; Rossi, E. *Tetrahedron* **2006**, *62*, 3033.

(3) For a useful review on the electrophile-promoted nucleophilic ring closure reactions of alkynes, see: Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.

(4) For examples of monocyclization processes involving related diynes, see: (a) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron* **2008**, *64*, 53. (b) Vinogradova, O. V.; Sorokoumov, V. N.; Balova, I. A. *Tetrahedron Lett.* **2009**, *50*, 6358. (c) Danilkina, N. A.; Bräse, S.; Balova, I. A. *Synlett* **2011**, 517. (d) Vinogradova, O. V.; Balova, I. A.; Popik, V. V. *J. Org. Chem.* **2011**, *76*, 6937.

(5) 1-(*o*-Ethynylaryl)ureas have been shown to undergo either 6-*exo*-dig or 5-*endo*-dig cyclization reactions depending on the choice of catalyst and reaction conditions: Gimeno, A.; Medio-Simón, M.; Ramírez de Arellano, C.; Asensio, G.; Cuenca, A. B. *Org. Lett.* **2010**, *12*, 1900.

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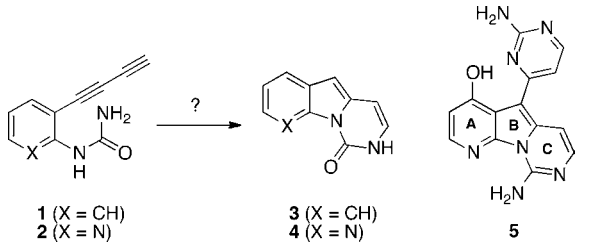
of this twofold cyclization process, thereby providing various analogues of the ABC-heterotricyclic framework associated with, for example, the potent antitumor agent variolin B (**5**).[6,7]

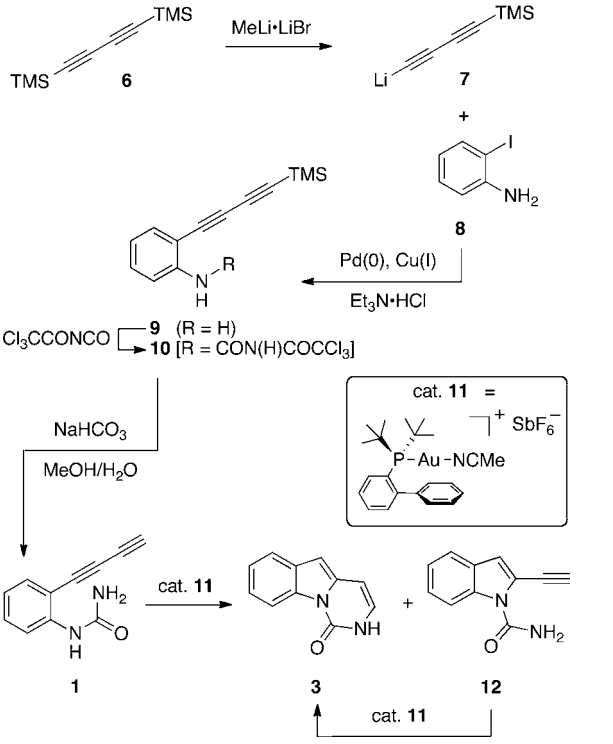


1 (X = CH)
2 (X = N)
3 (X = CH)
4 (X = N)
5

Figure 1. Proposed twofold cyclization process.

The substrate **1** required for initial studies of the proposed twofold cyclization process was readily prepared according to the reaction sequence shown in Scheme 1. Thus, the commercially available diyne **6** was treated with MeLi•LiBr and the lithium diacetylide **7** so-formed was subjected to Sonogashira cross-coupling with *o*-iodoaniline (**8**) and thereby generating the *o*-(buta-1,3-diyn-1-yl-)-substituted aniline **9** (81%).[8] Reaction of compound **9** with trichloroacetyl isocyanate afforded the corresponding *N*-acyl-*N*′-arylurea **10** (96%), the structure of which was confirmed by single-crystal X-ray analysis.[9] Upon treatment with sodium bicarbonate in aqueous methanol, compound **10** was converted into the target **1** (76%), the spectral data for which were in complete accord with the assigned structure. A variety of conditions were then examined in an effort to effect the conversion of this compound into isomer **3**.[10] Echavarren's gold(I) catalyst **11**[11] proved most useful in this regard[12] [see the Supporting Information (SI) for details]. While initial experiments lead to a chromatographically separable mixture of mono- and bis-cyclized materials, viz. compounds **12** and **3** respectively, conditions were readily established (5 mol % **11**, THF, 100 °C, microwave radiation, 1 h) for obtaining the latter product exclusively and in 78% yield. The structure of pyrimido[1,6-*a*]indol-1(2*H*)-one (**3**) was confirmed by single-crystal X-ray analysis.[9] Furthermore, subjection of compound **12** to the reaction conditions defined above gave product **3** in 75% yield.

Scheme 1



This novel conversion was readily extended to a range of *o*-(buta-1,3-diyn-1-yl-)-substituted *N*-aryl ureas (**13**–**28**, Figure 2), thereby giving the corresponding pyrimido-[1,6-*a*]indol-1(2*H*)-ones (**29**–**41**)[9] or the related 1*H*-imidazo-[1,5-*a*]indol-3(2*H*)-ones (**42** and **43**)[13] in uniformly acceptable yields (Table 1). The substrates used in these studies were prepared by methods similar to those shown in Scheme 1. Full details are provided in the SI. There are several noteworthy outcomes associated with the tabulated results. In particular, a range of substituents are tolerated at the C4 and C5 positions on the substrate (entries 1–9, Table 1). Furthermore, the phenyl-capped diynes **22** and **25**, which can be prepared by Sonogashira cross-coupling of compounds **1** and **16** with iodobenzene, also engage in the anticipated twofold cyclization process (entries 10 and 13) and thereby forming the 3-phenylpyrimido-[1,6-*a*]indol-1(2*H*)-ones **38** and **39**, respectively. The corresponding TMS-capped systems **23** and **24**, which are readily derived from aniline **9** or its 4-*tert*-butyl analogue using minor variations on the reaction sequence shown in Scheme 1, also undergo the expected cyclization process

(6) (a) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987. (b) Trimurtulu, G.; Faulkner, D. J.; Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993.

(7) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080.

(8) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3711.

(9) Details are provided in the Supporting Information (SI).

(10) The parent compound **3** has not been reported previously, but various derivatives, including biologically active ones, have been described; see, for example: (a) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854. (b) Facoetti, D.; Abbiati, G.; d'Avolio, L.; Ackermann, L.; Rossi, E. *Synlett* **2009**, 2273. (c) Nakamura, I.; Sato, Y.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 4198. (d) Wang, Z.-J.; Yang, J.-G.; Yang, F.; Bao, W. *Org. Lett.* **2010**, *12*, 3034.

(11) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455.

(12) For useful points-of-entry into the literature on gold-catalyzed cyclization reactions of alkynes, see: (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (b) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644. (c) Hashmi, A. S. K.; Lauterbach, T.; Nösel, P.; Vilhelmsen, M. H.; Rudolph, M.; Rominger, F. *Chem.—Eur. J.* **2013**, *19*, 1058. (d) Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2593. (e) Reference 1c.

(13) 1*H*-Imidazo[1,5-*a*]indol-3(2*H*)-ones are rare: Katritzky, A. R.; Singh, S. K.; Bobrov, S. *J. Org. Chem.* **2004**, *69*, 9313.

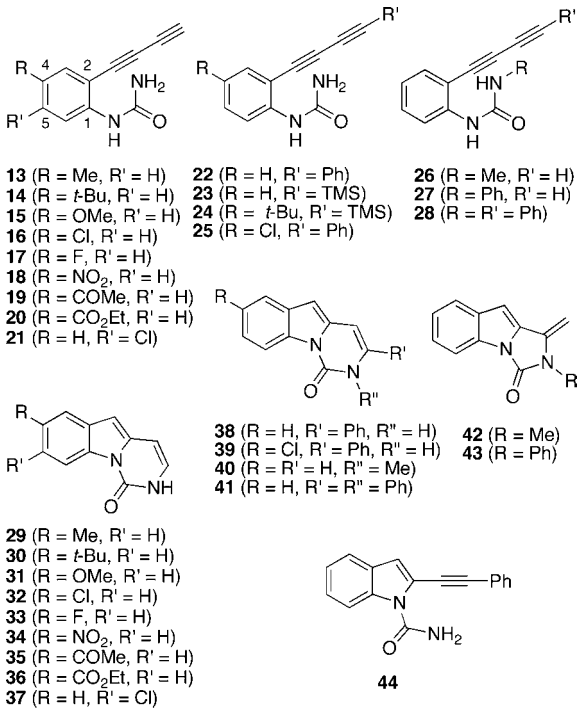


Figure 2. Substrates and products associated with the title process.

Table 1. Outcomes of the Au(I)-Catalyzed Cyclization Reactions of Compounds **13**–**27**[a]

entry	substrate	product(s)	yield (%)
1	**13**	**29**	56
2	**14**	**30**	40
3	**15**	**31**	39
4	**16**	**32**	70
5	**17**	**33**	62
6	**18**	**34**	49
7	**19**	**35**	59
8	**20**	**36**	61
9	**21**	**37**	67
10	**22**	**38**	60
11	**23**	**3**	75
12	**24**	**30**	56
13	**25**	**39**	65
14	**26**	**40** + **42**	28 (of **42**)
15	**27**	**43**	56
16[b]	**28**	**41**	68

[a] Reactions carried out under microwave irradiation in THF at 100 °C for 1 h using 5 mol % of **11** as catalyst. [b] This conversion was effected using 10 mol % of catalyst **11** at 100 °C for 2 h.

(entries 11 and 12), but at some point the associated silicon-based group is lost and so compounds **3** and **30**, respectively, are the observed products. Additional substituents on the urea moiety appear capable of changing the mode of the second cyclization step. Thus, when the readily obtained *N,N'*-disubstituted ureas **26** and **27** were subjected to the normal conditions (entries 14 and 15), then the major products proved to be the 1*H*-imidazo[1,5-*a*]indol-3(2*H*)-ones **42** and **43** although the former product was accompanied by quantities (22%) of the isomeric 2-phenylpyrimido[1,6-*a*]indol-1(2*H*)-one **40**. In contrast, subjection of the diphenyl-substituted system **28** to the same conditions afforded the pyrimido[1,6-*a*]indol-1(2*H*)-one **41** exclusively (and in 68% yield).

Once again, the stepwise nature of the cyclization of these substrates is supported by the observation that when compound **22** was treated with 5 mol % of catalyst **11** at 18 °C for 24 h, then a chromatographically separable mixture of compound **38** (21%) and the isomeric indole **44** (72%) was obtained. Resubjection of the latter product to reaction with catalyst **11** under the usual conditions (1 h at 100 °C) then gave pyrimido[1,6-*a*]indol-1(2*H*)-one **38** in 93% yield.

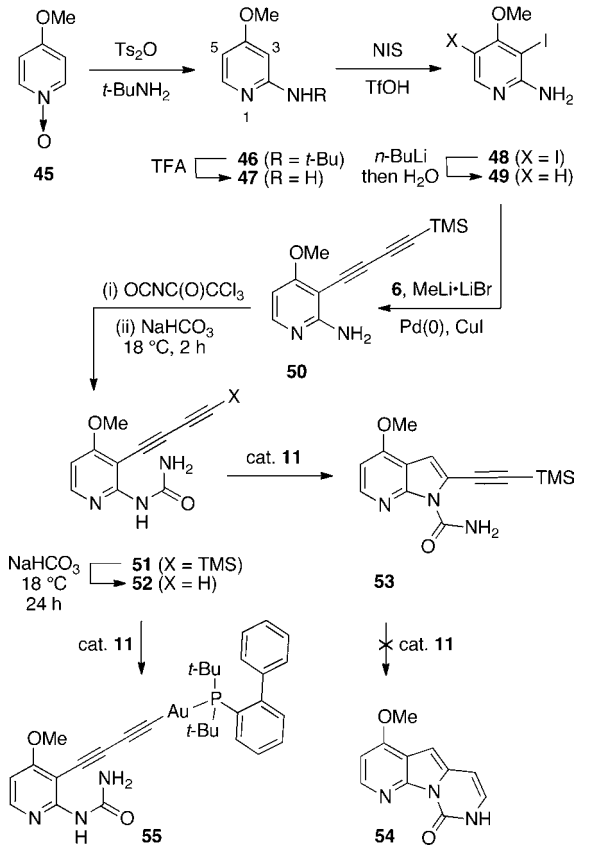
Efforts to deploy the cyclization processes detailed above in the assembly of the ABC-ring system of variolin B are outlined in Scheme 2. A substrate of the general form **2** suitable for examination of the proposed Au(I)-catalyzed tandem cyclization process was prepared by first treating commercially available 4-methoxypyridine *N*-oxide (**45**) with tosic anhydride in the presence of *tert*-butylamine[14] and thereby generating the 2-aminopyridine **46** in 61% yield. Cleavage of the *tert*-butyl group within this product was readily accomplished using trifluoroacetic acid, and the primary amine **47** so-formed (73%) was reacted with 2.5 mol equiv of *N*-iodosuccinimide (NIS) in the presence of triflic acid to give the di-iodinated derivative **48** in 70% yield.[15] Treatment of this last compound with *n*-butyllithium in THF at −78 to 18 °C followed by quenching with water resulted in selective removal of the C5-iodine and formation of the monoiodide **49** which was obtained as a white, crystalline solid in 74% yield. Sonogashira cross-coupling of compound **49** with the acetylide anion derived from the reaction of compound **6** with MeLi•LiBr gave diyne **50** (63%) that, upon successive treatment with trichloroacetyl isocyanate and then methanolic sodium bicarbonate at 18 °C for 2 h, afforded the TMS-capped compound **51** in 24% yield. In contrast, extended exposure (24 h) of the product from the first step to sodium bicarbonate gave the terminal diyne **52** in 75% yield. Treatment of the former product (viz. **51**) with catalyst **11** in THF at 60 °C for 5 h afforded the monocyclized product **53** in 40% yield. However, all attempts to engage this compound in a second cyclization reaction so as to generate the target tricyclic system **54**, failed. In particular, subjection of compound **53** to the more forcing cyclization conditions used to effect the various forms of the conversion **1** → **3** detailed above (Table 1) only resulted in loss of the carboxamide group[16] in this case. On the basis that the TMS-capping group in compounds **51** and **53** may be

(14) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554.

(15) Monoiodination of compound **47** under various conditions (see the SI) gave the 5-iodo-derivative, the structure of which was established by single-crystal X-ray analysis.

(16) The structure of the product indole was confirmed by single-crystal X-ray analysis (see the SI).

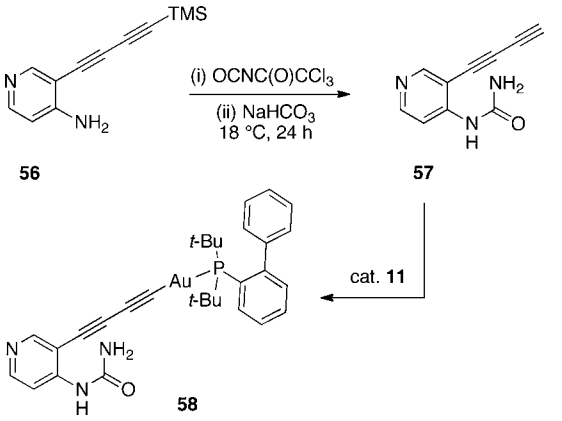
Scheme 2



inhibiting the second cyclization process, the terminal alkyne **52** was treated with the catalyst **11**, but in this instance the only isolable product of reaction was the gold acetylide **55** (62% based on **11**).

We speculated that the conversion **53** → **54** may be failing because of the chelating capacities of the 7-azaindole nitrogen and the adjacent *N*-1 carboxamide residues within the former compound. Accordingly, the behavior of a 4-aminopyridine-derived system was investigated. The substrate required for such an investigation was prepared by the simple means shown in Scheme 3 and which included treatment of the readily obtained (see the SI) TMS-capped diyne **56** with trichloroacetyl isocyanate and then methanolic sodium bicarbonate and so giving target **57** (95%). However, treatment of the latter compound with catalyst **11** only gave the Au(I)–acetylide complex **58** (90% based on **11**), the structure of which was confirmed by single-crystal X-ray analysis.[9] In other attempts to effect the desired twofold cyclization of compounds such as **51**, **52**, **56**, and **57**, efforts were made to convert them into their corresponding *N*-oxides and/or to complex them with various acids prior to their exposure to catalyst **11**. However, none of these resulted in the formation of the target tricyclic ring system.

Scheme 3



The origins of the divergent behaviors of compound **1** and its aza-analogues **52** and **57** are the subject of ongoing investigations, the results of which will be reported in due course.

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Supporting Information Available. Full experimental procedures; data derived from the single-crystal X-ray analyses of compounds **3**, **10**, **36**, **43**, the 5-iodo derivative of compound **47**, the indole from **53** (form 1), the indole from **53** (form 2) and **58** (CCDC numbers 876496–876503, respectively); ^{1}H and ^{13}C NMR spectra of compounds **1**, **3**, **10**, **12**–**44**, **47**–**53**, and **55**–**58**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.