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New Synthetic Approach for the Construction of Multisubstituted 2-Acyl Furans by the IBX-Mediated Cascade Oxidation/Cyclization of *cis*-2-En-4-yn-1-ols (IBX = 2-Iodoxybenzoic Acid)

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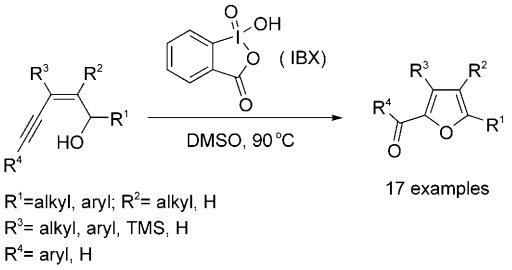
Hypervalent iodine compounds have been proved to be mild and selective oxidizing agents in an impressive array of synthetic methodologies and have received much attention in recent years.[1] 2-Iodoxybenzoic acid (IBX, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) was first synthesized in 1893; however, it was rarely used in organic synthesis until 1983 when Dess and Martin transformed IBX into the highly soluble Dess–Martin periodinane (DMP).[2] In 1994, Frigero and Santagostino reported that IBX could be readily dissolved in dimethyl sulfoxide (DMSO) and served as valuable oxidant toward a variety of alcohols.[3] Since then, a great deal of work has been done in IBX-mediated transformations with regards to mechanistic and synthetic aspects.[1,4] Generally, IBX is used as an efficient and mild oxidizing reagent, for example, for the mild oxidative cleavage of oximes and tosyl hydrazones,[4a] oxidation of amines to imines,[4b] oxidative rearrangement of tertiary allylic alcohols,[4c] oxidation of silyl enol ethers to enones,[4d] α-hydroxylation of carbonyl compounds,[4e] oxidative multicomponent reactions,[4f–h] and so forth. IBX also operates as a single-electron-transfer oxidant, such as in benzylic oxidation.[5a] However, IBX-induced annulation strategies are quite limited. A remarkable work has been reported by Nicolaou et al.; they have shown that IBX can promote the cyclization of unsaturated anilides, carbamates, and ureas via amide-centered radicals to form novel and biologically important N-heterocyclic compounds.[5b–d] Nevertheless, there is no report for IBX-assisted cyclization of alkynes,[6] to the best of our knowledge. In this paper, we report for the first time of IBX-promoted cascade oxidation/cyclization of *cis*-2-en-4-yn-1-ols, which represents an efficient and diversity oriented protocol for the convergent construction of substituted 2-acyl furans. 2-Acyl furans and furfurals are of significant synthetic interest, since they can be applied as flavouring agents, perfume components, or as useful and versatile synthetic intermediates for access to the condensed furanic ring systems that shows widespread biological activity,[7] such as Dantrolene analogues,[7a] anti-malarial agents,[7b] Phosphoinositide 3-Kinase γ inhibitors,[7c] HIV-1 integrase binding inhibitors,[7d] and so forth. However, the synthetic route for multisubstituted 2-acyl furans in a regioselective manner is rare (Scheme 1).[8]



Scheme 1. IBX-mediated formation of 2-acyl furans from *cis*-enynols.

Recently, we have reported an efficient synthetic approach to furans and stereo-defined dihydrofurans via gold-catalyzed cyclization of (*Z*)-2-en-4-yn-1-ols.[9] During our studies of new processes for heterocycle formation, we found that (*Z*)-enynol **1a** reacted with IBX in DMSO at room temperature to afford the normal oxidation product **2a** in 81% yield (Scheme 2). To our delight, when the reaction temperature was increased to 90 °C, 2-benzoyl-5-phenylfuran (**3a**) was formed in 79% yield, while the intermediate of **2a** was completely consumed. Decreasing the reaction temperature to 50 °C resulted in an incomplete transformation to **3a** (26 h, **2a**/**3a** = 3.6:1). Addition of five equivalents of H_2O resulted in a decreased yield of **3a** (NMR yield:

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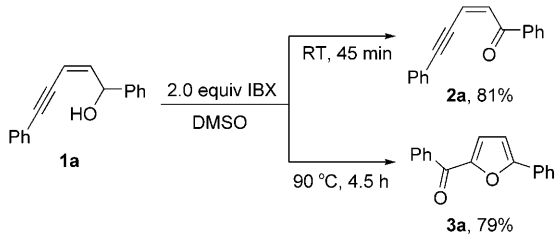
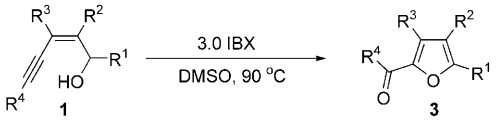


Scheme 2. Reactions of (*Z*)-enynol **1a** with IBX.

53%, 9 h). The use of DMP instead of IBX only afforded a complicated reaction mixture as observed by ^{1}H NMR spectroscopy at 0°C for 1.5 h in CH_2Cl_2.

As illustrated in Tables 1 and 2, the present method could be applied successfully to a wide range of *cis*-enynols bearing various substituents at C1–C5. The cyclization of enynols **1a**–**1f**, which were not substituted at C2 and C3, were investigated first. We found that the substituents Br, OMe and Cl on the aromatic rings at C1 and C5 were well tolerated during the reaction, furnishing the corresponding furans **3b**–**3e** in 64%–86% yield with relatively long reaction times of 15–18 h (Table 1, entries 2–5). Introducing an alkyl group at C1 also afforded furan **3f** in a satisfactory yield of 60% at 90°C (Table 1, entry 6). When enynol **1g** with an alkyl substituent at C5 was employed, the desired 2-acyl furan was not observed; instead a mixture of structurally unidentified products were formed (Table 1, entry 7). The results of enynols **1h**–**1k** bearing an additional alkyl substituent at C2 are highly dependent on the substituents on C1. Enynol **1h** substituted both at C1 and C2 with alkyl groups resulted in a lower yield of **3h** (41%, Table 1, entry 8). We envisioned that this may due to the lower stability of dialkyl-substituted furan **3h** under IBX oxidation conditions. However, changing the alkyl substituent at C1 to aryl groups resulted in good yields of **3i**–**3k** (68–85%, Table 1, entries 9–11). The structure of the 2-acyl furans was further confirmed by X-ray crystallographic analysis of **3c**[10] and 2D NMR spectrum of **3k**.

Table 1. Formation of 2-acyl furans mediated by IBX.

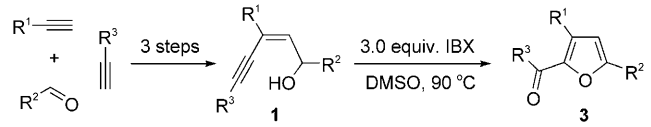


	Enynol	R^1	R^2	R^3	R^4	*t* [h]	Product	Yield [%][a]
1	**1a**	Ph	H	H	Ph	4.5	**3a**	79[b]
2	**1b**	*p*-BrC_6H_4	H	H	Ph	18	**3b**	64[c]
3	**1c**	*p*-$MeOC_6H_4$	H	H	Ph	15	**3c**	72
4	**1d**	*p*-ClC_6H_4	H	H	*p*-$MeOC_6H_4$	15	**3d**	67
5	**1e**	*p*-ClC_6H_4	H	H	*p*-ClC_6H_4	15	**3e**	86
6	**1f**	Et	H	H	Ph	4	**3f**	60[b]
7	**1g**	Ph	Et	H	Bu	4	–[d]	
8	**1h**	Et	Et	H	Ph	7	**3h**	41
9	**1i**	Ph	Et	H	Ph	10	**3i**	68
10	**1j**	*p*-ClC_6H_4	Et	H	Ph	12	**3j**	85
11	**1k**	*p*-$MeOC_6H_4$	Et	H	Ph	12	**3k**	81

[a] Isolated yields. Unless otherwise noted, 3.0 equiv IBX was used. [b] 2.0 equiv IBX was used. [c] 49% yield when 2.0 equiv IBX was used. [d] A mixture of structurally unidentified products was observed.

(*Z*)-Enynols bearing a substituent at the C3 position were prepared by the Sonogashira coupling reaction of iodinated allylic alcohols with terminal alkynes. The iodide precursors were conveniently synthesized from the corresponding propargylic alcohols by their reaction with Red-Al (Red-Al = sodium bis(2-methoxyethoxy)aluminumhydride) followed by iodination of the organoaluminum intermediate.[11] Thus enynols **1l**–**1q** can be easily constructed by three steps from two alkynes and one aldehyde. The following IBX-mediated cyclization represents a diversity oriented protocol for the convergent construction of 3,5-disubstituted-2-acyl furans. As shown in Table 2, the aryl, alkyl, and TMS groups at C3 in enynol **1** are all compatible with this cyclization reaction, furnishing the corresponding products **3l**–**3q** in 40–78% yields. It should be noted that in the case of **3l**, a decreased yield of 31% was observed at a prolonged reaction time (6.5 h). Interestingly, when terminal alkynes of **1o**–**1q** were used, 3,5-disubstituted-2-furaldehydes **3o**–**3q** were formed in 40–78% yields (Table 2, entries 4–6). However, for enynols substituted both at C2 and C3, for example, in the case of (*Z*)-2,3-diethyl-5-(4-methoxy-phenyl)-1-phenyl-pent-2-en-4-yn-1-ol (**1r**), only a mixture of 2-acyl furan **3r** and oxidation product of ketone **2r** with a ratio of 1:1.8 (90°C, 13 h) was isolated in a combined yield of 72%.

Table 2. Formation of 3,5-disubstituted 2-acyl furans mediated by IBX.



	Enynol	R^1	R^2	R^3	*t* [h]	Product	Yield [%][a]
1	**1l**	Ph	Ph	Ph	3	**3l**	59
2	**1m**	Bu	Ph	Ph	4	**3m**	70
3	**1n**	TMS	Ph	Ph	4	**3n**	70
4	**1o**	Ph	Ph	H	3	**3o**	78
5	**1p**	Bu	Ph	H	3	**3p**	76
6	**1q**	Ph	*p*-ClC_6H_4	H	3	**3q**	40

[a] Isolated yields.

Although further investigations to clarify the reaction mechanism are needed, a tentatively suggested reaction pathway is shown as follows (Scheme 3): first, an enynone **2a** is formed by oxidation of **1a**. In the next step, IBX may act as an electrophile to promote the cycloaddition of carbonyl group to the alkyne moiety. Thus, an *anti*-5-*exo*-dig cyclization is resulted to give **4**. This is followed by addition of hydroxyl group to the exocyclic double bond to form **5**, which subsequently decomposes to give 2-acyl furan **3a** and 1-iodosobenzoic acid (IBA).

To support the reaction mechanism, the reaction of enynone **2a** and IBX (1.2 equiv) was carried out. The desired product **3a** was obtained in 80% yield (Scheme 4, top). It is

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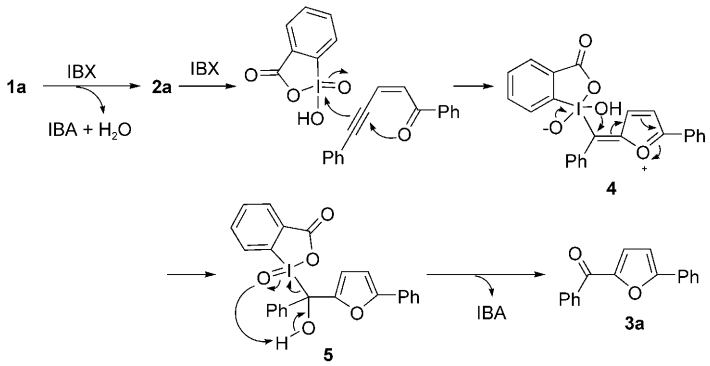
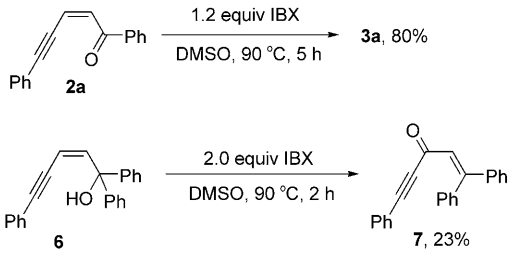


Scheme 3. Proposed reaction mechanism for the formation of 2-acyl furans.



Scheme 4. Reactions of **2a** and **6** with IBX.

worth noting that in the absence of IBX, **3a** could not be detected, only a partial decomposition of enynol **1a** was observed. IBA could also be served as an electrophile, since the same product **3a** was obtained at 90 °C in 57 % yield from **2a** in the presence of 1.2 equivalents of IBA, although a longer reaction time (ca. 23 h) was required. When tertiary alcohol **6** was employed under oxidation conditions, to our surprise, ketone **7** was isolated in 23 % yield, which was formed through an IBX-mediated oxidative rearrangement (Scheme 4, bottom).[4c]

In conclusion, we have developed a new approach for the construction of multisubstituted 2-acyl furans through IBX-mediated oxidation/cyclization in DMSO. The furan derivatives are useful synthetic intermediates, especially for access to the compounds that bearing biological activity. Further studies to elucidate the reaction mechanism and to extend the scope of synthetic utility are in progress in our laboratory.

Experimental Section

A typical procedure for IBX-mediated cyclization of (*Z*)- 3-butyl-1,5-diphenyl-pent-2-en-4-yn-1-ol (1m): IBX (3.0 equiv, 296 mg, 1.05 mmol) was added to a solution of (*Z*)-enynol **1m** (102 mg, 0.35 mmol) in DMSO (1.0 mL). The resulting solution was stirred at 90 °C until the reaction was complete, as monitored by thin-layer chromatography. After the reaction, the precipitate of IBA (probably) was removed by filtration, and the filtrate was diluted with water and extracted with diethyl ether. The aqueous phase was extracted with diethyl ether three times. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford the 2-acyl furan derivative **3m** in 70 % yield. ^{1}H NMR ($CDCl_3$, Me_4Si): $\delta = 0.96$ (t, $J = 7.4$ Hz, 3H), 1.41–1.48 (m, 2H), 1.63–1.71 (m, 2H), 2.96 (t, $J = 7.7$ Hz, 2H), 6.77 (s, 1H), 7.32–7.42 (m, 3H), 7.47–7.56 (m, 3H), 7.69–7.72 (m, 2H), 8.06–8.09 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 13.90$, 22.51, 26.08, 31.59, 109.73, 124.76, 128.09, 128.81, 128.92, 129.41, 129.48, 131.89, 138.24, 140.50, 147.18, 155.54, 183.21 ppm; IR (neat): $\tilde{\nu} = 3064$, 2957, 1637, 1476, 1291, 907, 691 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{21}H_{20}O_2$: 304.1463; found: 304.1459.

Acknowledgements

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Keywords: cyclization · enynols · furans · iodoxybenzoic acid · oxidation

[1] For reviews: a) P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123; b) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523; c) T. Wirth, *Angew. Chem.* **2001**, *113*, 2893; *Angew. Chem. Int. Ed.* **2001**, *40*, 2812; d) H. Tohma, Y. Kita, *Adv. Synth. Catal.* **2004**, *346*, 111; e) T. Wirth in *Organic Synthesis Highlights V* (Eds.: H. G. Schmalz, T. Wirth), Wiley-VCH, Weinheim, **2003**, pp. 144–150; f) U. Ladziata, V. V. Zhdankin, *Synlett* **2007**, 527; g) T. Wirth, *Angew. Chem.* **2005**, *117*, 3722; *Angew. Chem. Int. Ed.* **2005**, *44*, 3656.

[2] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277.

[3] a) M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019; b) M. Frigerio, M. Santagostino, S. Sputore, G. Palmisano, *J. Org. Chem.* **1995**, *60*, 7272.

[4] For selected papers, see: a) D. S. Bose, P. Srinivas, *Synlett* **1998**, 977; b) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *Angew. Chem.* **2003**, *115*, 4211; *Angew. Chem. Int. Ed.* **2003**, *42*, 4077; c) M. Shibuya, S. Ito, M. Takahashi, Y. Iwabuchi, *Org. Lett.* **2004**, *6*, 4303; d) K. C. Nicolaou, D. L. F. Gray, T. Montagnon, S. T. Harrison, *Angew. Chem.* **2002**, *114*, 1038; *Angew. Chem. Int. Ed.* **2002**, *41*, 996; e) S. F. Kirsch, *J. Org. Chem.* **2005**, *70*, 10210; f) P. Fontaine, A. Chiaroni, G. Masson, J. Zhu, *Org. Lett.* **2008**, *10*, 1509; g) T. Ngouansavanh, J. Zhu, *Angew. Chem.* **2007**, *119*, 5877; *Angew. Chem. Int. Ed.* **2007**, *46*, 5775; h) T. Ngouansuvanh, J. Zhu, *Angew. Chem.* **2006**, *118*, 3575; *Angew. Chem. Int. Ed.* **2006**, *45*, 3495; i) J. T. Su, W. A. Goddard III, *J. Am. Chem. Soc.* **2005**, *127*, 14146.

[5] a) K. C. Nicolaou, P. S. Baran, Y. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 3183; b) K. C. Nicolaou, Y. L. Zhong, P. S. Baran, *Angew. Chem.* **2000**, *112*, 639; *Angew. Chem. Int. Ed.* **2000**, *39*, 625; c) K. C. Nicolaou, P. S. Baran, Y. L. Zhong, J. A. Vega, *Angew. Chem.* **2000**, *112*, 2625; *Angew. Chem. Int. Ed.* **2000**, *39*, 2525; d) K. C. Nicolaou, P. S. Baran, Y. L. Zhong, S. Barluenga, K. W. Hunt, R. Kranich, J. A. Vega, *J. Am. Chem. Soc.* **2002**, *124*, 2233.

[6] For the reaction of hypervalent iodine reagent with alkynes, see a) B. Crone, S. F. Kirsch, *Chem. Commun.* **2006**, 764; b) Y. Kita, T. Yakura, H. Terashi, J. Haruta, Y. Tamura, *Chem. Pharm. Bull.* **1989**, *37*, 891; c) R. M. Moriarty, R. Penmasta, A. K. Awasthi, I. Prakash, *J. Org. Chem.* **1988**, *53*, 6124.

[7] a) T. Hosoya, H. Aoyama, T. Ikemoto, Y. Kihara, T. Hiramatsu, M. Endo, M. Suzuki, *Bioorg. Med. Chem.* **2003**, *11*, 663; b) J. Wiesner, A. Mitsch, H. Jomaa, M. Schlitzer, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2159; c) V. Pomel, J. Klicic, D. Covini, D. D. Church, J. P. Shaw, K. Roulin, F. Burgat-Charvillon, D. Valognes, M. Camps, C. Chabert, C. Gillieron, B. Françon, D. Perrin, D. Leroy, D. Gretener, A.

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Nichols, P. A. Vitte, S. Carboni, C. Rommel, M. K. Schwarz, T. Rückle, *J. Med. Chem.* **2006**, *49*, 3857; d) C. Mugnaini, S. Rajamaki, C. Tintori, F. Corelli, S. Massa, M. Witvrouw, Z. Debyser, V. Veljkovic, M. Botta, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5370; e) P. Villain-Guillot, M. Gualtier, L. Bastide, F. Roquet, J. Martinez, M. Amblard, M. Pugniere, J. P. Leonetti, *J. Med. Chem.* **2007**, *50*, 4195.

[8] For the synthesis of 2-acyl furans, see: a) A. P. Dunlop, F. N. Peters, *The Furan*, Reinhold, New York, **1953**, p. 421; b) C. H. Eugster, P. Bosshard, *Adv. Heterocycl. Chem.* **1966**, *7*, 400; c) R. Lombard, J. P. Stephan, *Bull. Soc. Chim. Fr.* **1958**, 1458; d) I. Francesconi, A. Patel, D. W. Boykin, *Synthesis* **1999**, 61; e) A. M. Bello, L. P. Kotra, *Tetrahedron Lett.* **2003**, *44*, 9271; f) M. Tinggaard, P. Hansen, P. K. Mogensen, O. Simonsen, J. Becher, *J. Heterocycl. Chem.* **1989**, *26*, 439; g) C. S. Davis, G. S. Lougheed, *J. Heterocycl. Chem.* **1967**, *4*, 153; h) N. Miyaura, ; A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; i) M. S. McClure, B. Glover, E. McSorley, A. Millar, M. H. Osterhout, F. Roschangar, *Org. Lett.* **2001**, *3*, 1677; j) R. Antonioletti, M. D′Auria, A. D. Mico, G. Piancatelli, A. Scettri, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1285.

[9] a) Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409; for Mo-catalyzed cyclization of epoxyalkynes prepared from enynols to furans, see: b) F. E. McDonald, C. C. Schultz, *J. Am. Chem. Soc.* **1994**, *116*, 9363.

[10] CCDC 692426 (**3c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] a) J. A. Marshall, B. A. Dehoff, *J. Org. Chem.* **1986**, *51*, 863; b) K. D. Kim, P. A. Magriotis, *Tetrahedron Lett.* **1990**, *31*, 6137; c) D. L. Romero, E. L. Fritzen, *Tetrahedron Lett.* **1997**, *38*, 8659; d) B. Gabriele, G. Salerno, E. Lauria, *J. Org. Chem.* **1999**, *64*, 7687.

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