EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Dihalohydration of Alkynols: A Versatile Approach to Diverse Halogenated Molecules

Authors: Samantha M Gibson, Jarryl D'Oyley, Joe Higham, Kate Sanders, Victor Laserna, Abil Aliev, and Tom David Sheppard

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800668

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800668

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

Dihalohydration of Alkynols: A Versatile Approach to Diverse Halogenated Molecules

Samantha M. Gibson, Jarryl M. D'Oyley, Joe I. Higham, Kate Sanders, Victor Laserna, Abil E. Aliev and Tom D. Sheppard*[a]

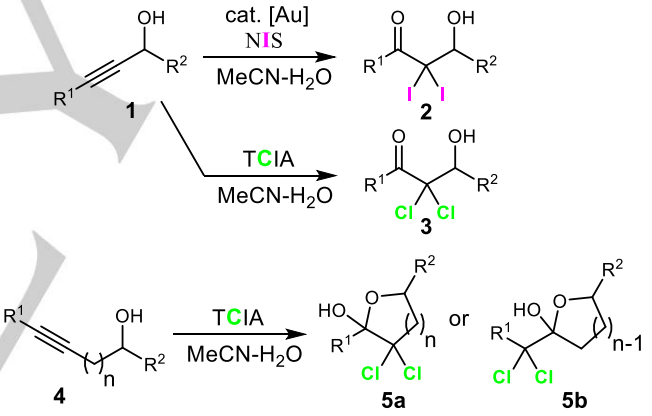
Dedication ((optional))

Abstract: In this paper we outline how dihalohydration reactions of propargylic alcohols can be used to access a wide variety of useful halogenated building blocks. A novel procedure for dibromohydration of alkynes has been developed, and a selection of dichloro and dibromo diols and cyclic ethers were synthesized. The dihalohydration of homo-propargylic alcohols provides a useful route to 3-halofurans, which were shown to readily undergo cycloaddition reactions under mild conditions. Finally, a novel ring-expansion of propargylic alcohols containing an alkynylcyclopropane provides access to halogenated alkenylcyclobutanes.

Introduction

Halogenated molecules play an important role in organic chemistry, both as synthetic targets themselves, and as useful reactants for a wide range of metal-catalysed reactions. For example, chlorinated and brominated functional groups are widely present in agrochemicals[1] and in flame retardants, although the latter are causing increasing environmental concerns.[2] They are also widely used starting materials for a range of organometallic cross-coupling methodologies.[3] Geminal dihalides have found application as carbene or carbenoid precursors which undergo reaction with metals (e.g. Zn), metal salts (e.g. $CrCl_2$), or organometallic reagents (e.g. Et_2Zn) to initiate cyclopropanation or olefination reactions.[4] Dihaloketones can also serve as useful precursors to enolates under reducing conditions.[5] The synthesis of functionalized geminal dihalides is rare, however, as most halogenation processes require harsh conditions. For example, geminal dihalides can be generated from carbonyl groups using deoxohalogenation reagents such as PCl_5, or via halogenation of the hydrazine or oxime derivatives.[6] Alternative methods via double carbometallation of alkynes are also incompatible with functionalized substrates.[7] We,[8] and others,[9-10] have observed that dihalohydration of alkynes offers a mild and preparatively useful approach to α,α-dihaloketones. These reactions usually proceed with high regioselectivity, and provide functionalized dihaloketones from readily available precursors. To date, however, the potentially interesting chemistry of these functionalized dihalides has not been explored in great detail.

As part of our ongoing interest in the development of novel chemistry employing propargylic alcohols,[11] we recently reported two methods for the dihalohydration of these systems **1** (Scheme 1), with a gold-catalysed iodination reaction providing access to previously unreported α,α-diiodo-β-hydroxyketones **2**, and a catalyst-free procedure using trichloroisocyanuric acid (TCIA) giving α,α-dichloro-β-hydroxyketones **3**. The latter procedure could also be extended to alkynols **4** giving access to dichlorolactols of general structure **5a** or **5b**.



Scheme 1. Previous work on the diiodohydration and dichlorohydration of alkynols.[8]

In this article, we describe the extension of this work to the dibromohydration of alkynols, and we also describe preliminary studies on the application of geminal dibromides and dichlorides in further synthetic transformations to access a diverse range of potentially useful halogenated molecules, many of which constitute previously unreported structural frameworks.

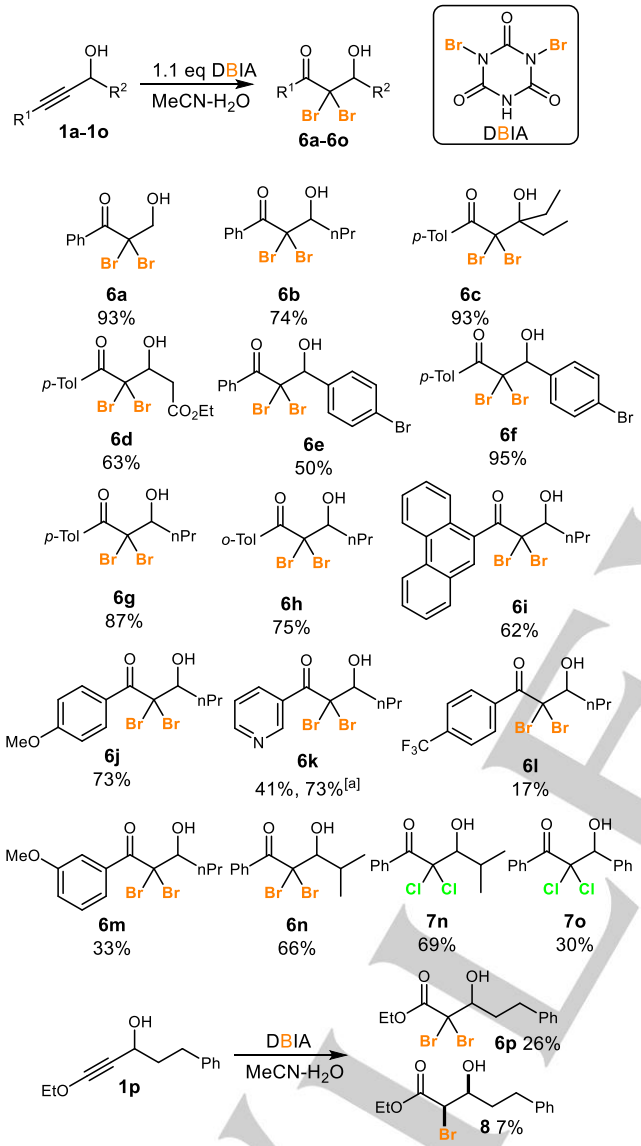
Results and Discussion

We set out to develop a method to convert readily accessible propargylic alcohols into the corresponding dibromohydroxyketones, whose properties remain relatively unexplored,[10] although they have recently been demonstrated as effective bioisosteres for hydrated ketones in quorum-sensing inhibitors.[12] The required dibromohydration of propargylic alcohols was achieved efficiently using dibromoisocyanuric acid

[a] Dr S. M. Gibson, Dr J. M. D'Oyley, Ms K. Sanders, Mr. J. I. Higham, Dr V. Laserna, Dr A. E. Aliev, Dr T. D. Sheppard
Department of Chemistry
University College London
Christopher Ingold Laboratories, 20 Gordon St, London, WC1H 0AJ, U.K.
E-mail: tom.sheppard@ucl.ac.uk
Homepage: www.tomsheppard.eu

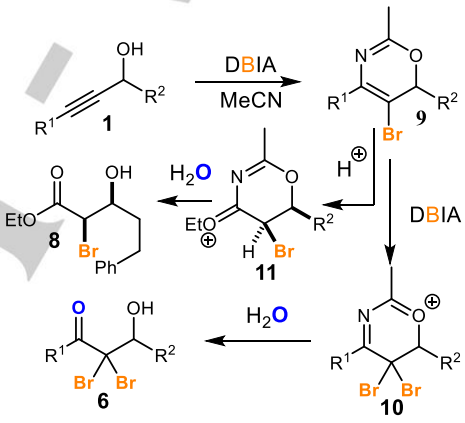
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

(DBIA)[13] under closely related conditions to our previously described dichlorohydration reaction.[8] Our initial experiments suggested that the reaction was more efficient with a higher proportion of water in the reaction medium (30% rather than 10% H_2O in MeCN).

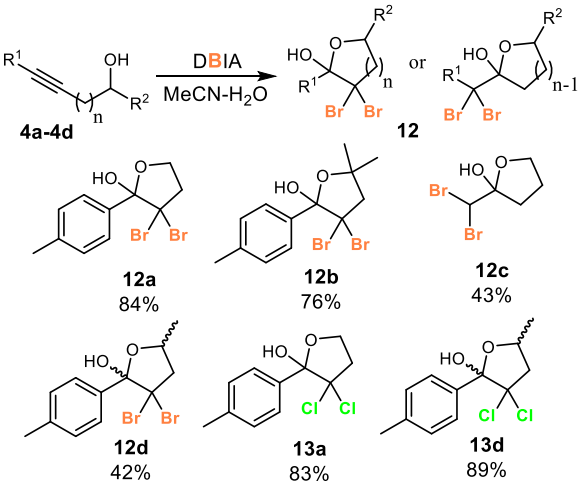


Scheme 2. Dibromohydration of propargylic alcohols.

Pleasingly, the reaction could be applied to primary, secondary and tertiary propargylic alcohols (Scheme 2, e.g. **6a**, **6b**, **6c**). As noted previously, an aryl group on the alkyne was necessary for efficient reaction. However, unsubstituted phenyl rings (**6a**, **6b**, **6e**, **6n**) and both electron rich (**6c**, **6d**, **6g**, **6h**, **6j**, **6m**) and electron deficient (**6l**, **6m**) aryl groups could be used, including examples bearing polyaromatic rings (**6i**) and a pyridine heterocycle (**6k**). A very electron-deficient benzene ring (**6l**) led to a low yield of the desired dibromide, however. Both aryl and alkyl chains could be incorporated as the R^2 substituent, including some functional groups (ester **6d**, aryl bromide **6e**-**6f**). The novel dichlorides **7n** and **7o** were also prepared using our previously reported dichlorohydration method. Interestingly, the dibromohydration of an ethoxyacetylene **1p** led to the formation of both the desired dibromide **6p** and the monobrominated compound **8**. The formation of this latter compound as a single diastereoisomer is consistent with our proposed mechanism in which the halogenation reaction proceeds via formation of heterocycle **9** through incorporation of a molecule of acetonitrile (Scheme 3). Heterocycle **9** can then undergo a second bromination to give dibromide **10** which then hydrolyses to yield the dibromoketone product **6**. Alternatively, protonation of highly electron rich heterocycle **9** (where R^1=OEt) may take place selectively on the least hindered side to give **11** which will yield *syn*-bromohydrin **8** as the major diastereoisomer after hydrolysis.

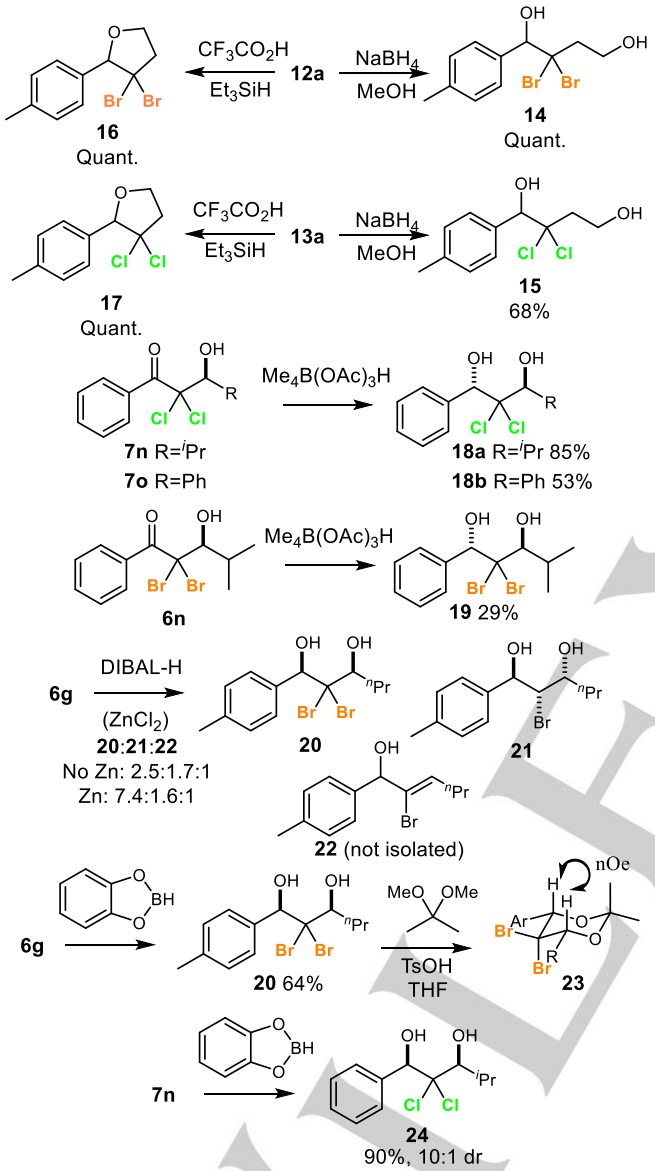


Scheme 3. Proposed mechanism for dibromohydration



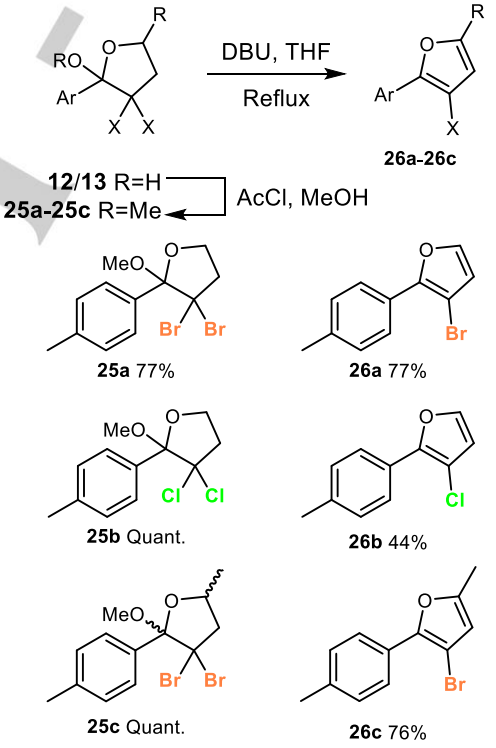
Scheme 4. Dibromohydration and dichlorohydration of extended alkynols.

The bromination reaction could be extended to the synthesis of dibromolactols **12a**-**12d** through reaction of extended alkynol derivatives (Scheme 4), including compounds containing primary (**12a**, **12c**), secondary (**12d**) and tertiary (**12b**) alcohols. Dichlorides **13a** and **13d** were also prepared via dichlorohydration of the alkynes using TCIA.



Scheme 5. Reduction of geminal dihalides to access halogenated diols and cyclic ethers.

With a selection of dihalohydroxyketones and dihalolactols in hand, we examined their reduction to access halogenated diols and cyclic ethers. Pleasingly, lactols **12a** and **13a** could be converted into the corresponding dihalo-1,4-diols **14**/**15** or dihalogenated tetrahydrofurans **16**/**17** through treatment with $NaBH_4$ or TFA/Et_3SiH respectively. Dichlorohydroxyketones **7n** and **7o** could readily be converted with high diastereoselectivity into the *anti*-dichlorodiols **18** via reduction with $Me_4NB(OAc)_3H$.[14] The same procedure was also used to access *anti*-bromodiol **19**. We next set out to investigate a complementary method to access the corresponding *syn*-dihalodiols. Reduction of **6g** with DIBAL-H in the presence or absence of $ZnCl_2$[15] led to the formation of a mixture of products including desired *syn*-diol **20**, monobrominated *anti*-diol **21**, and brominated allylic alcohol **22**, with the zinc chloride leading to an enhanced selectivity in favor of the desired diol **20**. An alternative reduction protocol using catechol borane[16] gave a mixture of *syn* and *anti* diols in 82% overall yield (82:18 dr), from which the desired *syn* diol **20** could be isolated in 64% yield. The stereochemistry of **20** was confirmed through formation of the acetonide **23** which displayed an nOe between the two axial protons indicated. Using the same method, dichlorohydroxyketone **7n** was converted into the corresponding *syn*-dichlorodiol **24** in 90% yield. Interestingly, dibromo-1,3-diols such as **19** and **20** have never previously been synthesised.[17]



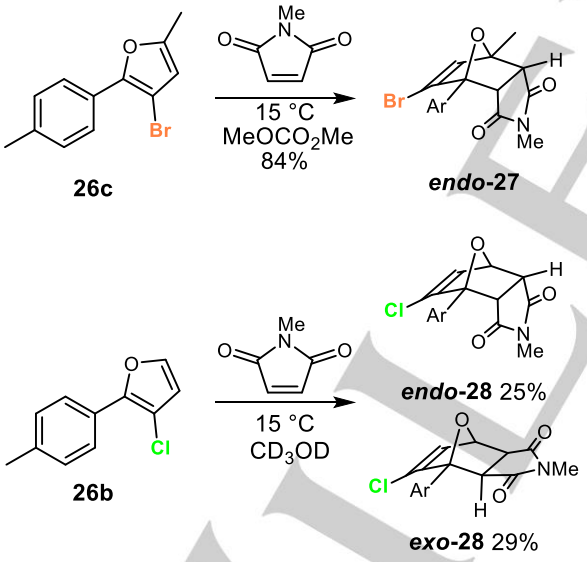
Scheme 6. Synthesis of 3-Halofurans

We envisaged that lactols such as **12a** could readily be converted into synthetically useful 3-halofurans[18] through formal elimination of water and HX. Attempts to convert **12a** directly into the 3-bromofuran were unsuccessful. However, further investigation determined that 3-halofurans could be successfully obtained through conversion of the lactols **12a**, **13a** and **13d** into the mixed ketal derivatives **25a-25c** with AcCl/MeOH, followed by basic elimination of methanol and HX. Using this sequence,

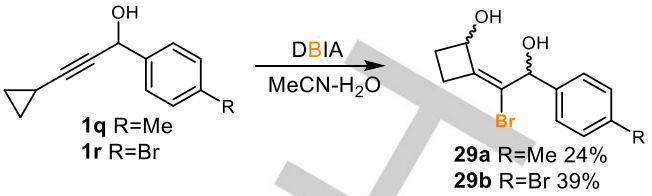
we were able to access 3-bromofuran **26a**, 3-chlorofuran **26b** and trisubstituted bromofuran **26c**; with complete control over the substitution pattern in the latter compound. This approach is complementary to routes employing ynones,[18a, b, e] providing access to a different regioisomer of the 3-halofuran.

We have previously reported that 3-alkoxyfurans are readily able to undergo Diels-Alder reaction with maleimides to provide *endo*-cantharimide derivatives, which are promising lead-like molecules for medicinal chemistry.[19] 3-Halofurans have been reported to show enhanced reactivity in intramolecular Diels-Alder reactions,[20-21] so we were therefore interested in exploring their reactivity with maleimides to access useful halogenated cantharimide derivatives. 3-Bromofuran **26c** gave the *endo* cantharimide **27** as a single diatereoisomer in excellent yield upon reaction with *N*-methylmaleimide. However, 3-chlorofuran **26b** gave a mixture of the separable *endo* and *exo* cantharimides **28** in moderate overall yield under similar conditions.

A further interesting transformation was uncovered upon attempted dibromination of cyclopropyl-containing propargylic alcohol **1q**, which yielded the vinylcyclobutane **29a** as the major product as a mixture of diastereoisomers. This reaction was extended to the synthesis of **29b**.[22] Although ring-expansion of cyclopropanes to cyclobutanes is precedented,[23] the direct ring-expansion of cyclopropylacetylenes has rarely been observed.[24]



Scheme 7. Cycloaddition reactions of 3-halofurans.



Scheme 8. Synthesis of cyclobutanes via ring-expansion of propargylic alcohols containing cyclopropylacetylenes.

Conclusions

We have reported a new method for the dibromohydration of alkynols to give dibromoketones that is applicable to a wide range of substrates, along with the extension of our previously reported dichlorohydration reaction to new substrates. The dihaloketones obtained from these reactions can be used to prepare structurally diverse halogenated molecules including dihalodiols, dihalogenated tetrahydrofurans, 3-halofurans, and halogenated cantharimides. We have also discovered a novel halogenation/ring expansion of alkynylcyclopropanes which provides alkenylcyclobutanes. Many of these classes of halogenated compound have never previously been prepared. Further work is underway to optimize these methods, and to explore the interesting properties of these structurally unusual molecules.

Experimental Section

Full experimental procedures for the preparation of all compounds, along with ^{1}H and ^{13}C spectra for all novel compounds can be found in the supporting information.

Acknowledgements

We would like to thank the UCL Department of Chemistry for providing an EPSRC studentship to SMG, the UCL Drug Discovery PhD Programme for providing an EPSRC studentship to JMD, the Leverhulme Trust for providing PDRA funding for VL (RPG-2017-221), and the EPSRC National Mass Spectrometry Facilty at Swansea University for assistance with analysis of some samples.

Keywords: Halogenation • Alkynes • Alcohols • Heterocycles • Ketones.

[1] a) P. Jeschke, *Pest Manag. Sci.* **2010**, *66*, 10; b) P. Jeschke, *Pest Manag. Sci.* **2017**, *73*, 1053.
[2] E. S. Beach, B. R. Weeks, R. Stern, P. T. Anastas, *Pur. Appl. Chem.* **2013**, *85*, 1611; K. D'Silva, A. Fernandes, M. Rose, *Crit. Rev. Environ. Sci. Technol.* **2004**, *34*, 141.
[3] a) P. G. Gildner,; T. J. Colacot, *Organometallics* **2015**, *34*, 5497; b) I. Hussain, J. Capricho,;M. A. Yawer, *Adv. Synth. Catal.* **2016,** *358*, 3320.

[4] a) L. T. Scott, W. D. Cotton, *J. Am. Chem. Soc.* **1973**, *95*, 2708; b) T. Okazoe, K. Takai, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 951.

[5] a) A. Takahashi, M. Shibasaki, *J. Org. Chem.* **1988**, *53*, 1227; b) C. Peppe, R. Pavão das Chagas, *Synlett* **2006**, 605; For use in [4+3] cycloadditions, see: c) R. S. Grainger, R. B. Owoare, P. Tisselli, J. W. Steed, *J. Org. Chem.* **2003**, *68*, 7899; d) S. Sendelbach, R. Schwetzler-Raschke, A. Radl, R. Kaiser, G. H. Henle, H. Korfant, S. Reiner, B. Föhlisch, *J. Org. Chem.* **1999**, *64*, 3398.

[6] a) D. E. Armstrong, D. H. Richardson, *J. Chem. Soc.* **1933**, 496; b) T. Takeda, R. Sasaki, A. Nakamura, S. Yamauchi, T. Fujiwara, *Synlett* **1996**, 273; c) D. J. Dixon, S. V. Ley, S. Lohmann, T. D. Sheppard, *Synlett* **2005**, 481.

[7] L. Aufauvre, P. Knochel, I. Marek, *Chem. Commun.* **1999**, 2207.

[8] J. M. D'Oyley, A. E. Aliev, T. D. Sheppard, *Angew Chem. Int. Ed.* **2014**, *53*, 10747.

[9] a) G. A. Hiegel, C. D. Bayne, B. Ridley, *Synth. Commun.* **2003**, 33, 1997; b) J. Liu,W. Li, C.Wang, Y. Li, Z. Li, *Tetrahedron Lett.* **2011**, *52*, 4320; c) S. Madabhushi, R. Jillella, K. K. R. Mallu, K. R. Godala, V. S. Vangipuram, *Tetrahedron Lett.* **2013**, *54*, 3993; d) C. Shu, L. Li, C.-H. Shen, P.-P. Ruan, C.-Y. Liu, L.-W. Ye, *Chem. Eur. J.* **2016**, *22*, 2282; e) L. Hu, C. Che, Z. Tan, G. Zhu, *Chem. Commun.* **2015**, *51*, 16641; f) S. Sadhukhan, B. Baire, *Adv. Synth. Catal.* **2018**, *360*, 298.

[10] a) M. M. Aborways, W. J. Moran, *Tetrahedron Lett.* **2014**, *55*, 2127; b) A. Jovtscheff, S. L. Spassov, *Monatscheft. Chem.* **1967**, *98*, 2326; c) T. Inokuchi, S. Matsumoto, M. Tsuji, S. Torii, *J. Org. Chem.* **1992**, *57*, 5023 d) S. Sadhukhan, B. Baire, *ChemistrySelect* **2017**, *2*, 8500; e) G. Qiu, Y. Li, L. Ma, H. Zhou, *Org. Chem. Front.* **2017**, *4*, 1069.

[11] a) M. N. Pennell, M. G. Unthank, P. Turner, T. D. Sheppard, *J. Org. Chem.* **2011**, *76*, 1479; b) M. N. Pennell, P. G. Turner and T. D. Sheppard, *Chem. Eur. J.* **2012**, *18*, 4748; c) M. N. Pennell, M. P. Kyle, S. M. Gibson, L. Male, P. G. Turner, R. S. Grainger, T. D. Sheppard, *Adv. Synth. Catal.* **2016**, *358*, 1519; d) M. N. Pennell, R. W. Foster, P. G. Turner, H. C. Hailes, C. J. Tame, T. D. Sheppard, *Chem. Commun.* **2014**, *50*, 1302; e) E. Barreiro, A. Sanz-Vidal, E. Tan, S. -H. Lau, T. D. Sheppard, S. Díez-González, *Eur. J. Org. Chem.* **2015**, 7544.

[12] M. Guo, Y. Zheng, J. L. Terell, M. Ad, C. Opoku-Temeng, W. E. Bentley, H. O. Sintim, *Chem. Commun.* **2015**, *51*, 2617.

[13] *1,3-Dibromoisocyanuric Acid*, S. C. Virgil in *e-EROS Encyclopedia of Reagents for Organic Synthesis* (Ed.: P. L. Fuchs), John Wiley & Sons, **2001**.

[14] a) A. K. Saksena, P. Mangiaracina, *Tetrahedron Lett.* **1983**, *24*, 273; b) D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560.

[15] M. Kuroboshi, T. Ishihara, *Bull Chem. Soc. Jpn.* **1990**, *63* 1185.

[16] D. A. Evans, A. H. Horveda, *J. Org. Chem.* **1990**, *55*, 5190.

[17] A Reaxys® search for acyclic 2,3-dibromo-1,3-diols returned no hits (5th Feb 2018); The only acyclic *syn*-2,3-dichloro-1,3-diol reported in the literature is the fungal natural product peyroisocoumarin B: Y. Zhao, D. Liu, P. Proksch, S. Yu, W. Lin, *Chem. Biodiversity* **2016**, *13*, 1186.

[18] a) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581; b) D. Obrecht, *Helv. Chim.Act.* **1989**, *72*, 447; c) A. Sniady, K. A. Wheeler, R. Dembinski, *Org. Lett.* **2005**, *7*, 1769; d) A. Sniady, M. S. Morreale, K. A. Wheeler, R. Dembinski, *Eur. J. Org. Chem.* **2008**, 3449; e) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991.

[19] R. W. Foster, L. Benhamou, M. J. Porter, D. -K. Bucar, H. C. Hailes, C. J. Tame, T. D. Sheppard, *Chem. Eur. J.* **2015**, *21*, 6107.

[20] a) A. Padwa, K. R. Crawford, C. S. Straub, S. N. Pieniazek, K. N. Houk, *J. Org. Chem.* **2006**, *71*, 5432; b) R. L. Rae, J. M. Żurek, M. J. Paterson, M. W. P. Bebbington, *Org. Biomol. Chem.* **2013**, *11*, 7946.

[21] For intermolecular Diels-Alder reactions of 3-halofurans, see a) A. McCluskey, S. P. Ackland, M. C. Bowyer, M. L. Baldwin, J. Garner, C. C. Walkom, J. A. Sakoff, *Bioorg. Chem.* **2003**, *31*, 68; b) R. N. Ram, N. Kumar, *Tetrahedron Lett.* **2008**, *49*, 799;

[22] The structure and alkene geometry of **29b** was confirmed by nOe studies and comparison of the observed coupling constants with values obtained from DFT calculations. Please see the supplementary information for further details; see also: A. E. Aliev, D. Courtier-Murias, *J. Phys. Chem. B.* **2007**, *111*, 14034.

[23] For ring expansion of unactivated cyclopropanes via a two-step sequence, see: R. Liu, M. Zhang, G. Winston-McPherson, W. Tang, *Chem. Commun.* **2013**, *49*, 4376;

[24] For direct ring-expansion of cyclopropylacetylenes under gold catalysis, see: a) S. Ye, Z. -X. Yu, *Org. Lett.* **2010**, *12*, 804

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Text for Table of Contents

((Insert TOC Graphic here: max. width: 5.5 cm; max. height: 5.0 cm; NOTE: the final letter height should not be less than 2 mm.))

Key Topic*

*Author(s), Corresponding Author(s)**

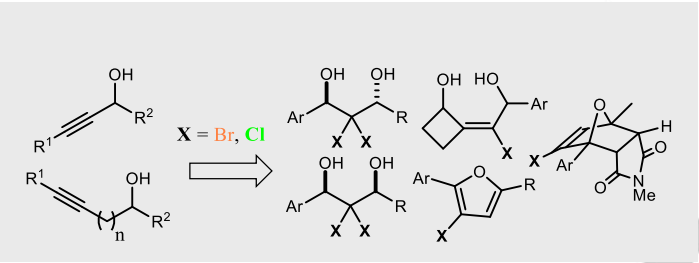
Page No. – Page No.

Title

*one or two words that highlight the emphasis of the paper or the field of the study

Layout 2:

FULL PAPER



Halogenated Molecules

*Samantha M. Gibson, Jarryl M. D'Oyley, Kate Sanders, Joe I. Higham, Victor Laserna, Abil E. Aliev and Tom D. Sheppard**

Page No. – Page No.

Dihalohydration of Alkynols: A Versatile Approach to Diverse Halogenated Molecules

*one or two words that highlight the emphasis of the paper or the field of the study