

Room-Temperature Electrophilic 5-*endo-dig* Chlorocyclization of Alk-3-yn-1-ones with the Use of Pool Sanitizer: Synthesis of 3-Chlorofurans and 5-Chlorofuropyrimidine Nucleosides

Adam Sniady,^[a] Marco S. Morreale,^[a] Kraig A. Wheeler,^[b] and Roman Dembinski*^[a]

Keywords: Alkynes / C–C coupling / Cyclizations / Halogenation / Heterocycles / Ketones / Nucleosides / Trichloroisocyanuric acid

The 5-*endo-dig* chlorocyclization of 1,4-disubstituted alk-3-yn-1-ones (propargylic ketones) with the use of trichloro-*s*-triazinetriene (trichloroisocyanuric acid, TCCA; 0.4 equiv.) in toluene, at room temperature, in the absence of base, provides 2,5-disubstituted 3-chlorofurans in high yields (79–96 %). The reaction can be accomplished by using commercially available swimming pool sanitizer. Selected 3-chlo-

rofurans were validated as a substrate for Suzuki–Miyaura coupling. In a similar manner, chlorocyclization of 5-alkynyl-2'-deoxyuridines produces 5-chlorofuropyrimidine nucleosides (76–83 %), which are analogues of potent antiviral agents.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

Introduction

The use of aryl chlorides has experienced recent attention due to new developments in efficient coupling methods. Even so, relatively few examples of arylation reactions employing heteroaryl chlorides have been reported.^[1] Furthermore, because of availability and enhanced reactivity in oxidative addition to transition metal complexes/catalysts, these reports are largely limited to the use of chlorides positioned *α* (*ortho*) to a heteroatom, which is predominantly nitrogen.^[2] Heteroaryl chlorides are readily available by direct chlorination of aromatic compounds. However, such reactions are frequently restricted to activated positions, or are less selective compared to other halogens.

Electrophilic halocyclization reactions offer an efficient and potent methodology that leads to functionalized heterocycles by tandem isomerization/halogenation processes.^[3] The electrophilic component serves as both a cyclization catalyst and halogen donor, thus creating a very effective process from the standpoint of material economy. Recently, several groups have extensively explored halocyclization reactions that yield functionalized heterocycles.^[4] Iodo, bromo, thio, and seleno derivatives can be produced with the use of halogen or pseudohalogen reagents such as molecular iodine, bromine, ICl, *N*-iodosuccinimide (NIS), IPy₂BF₄, *N*-bromosuccinimide (NBS), ArSBr, ArSCl, PhSeBr, PhSeCl, and BuTeBr₃. However, the chloroelectro-

philic reactions remain little explored, in part due to the diminished electrophilic character of chlorine compared to iodine or bromine.^[5,6]

We previously reported NIS/NBS electrophilic cyclizations leading to substituted furans and furopyrimidines.^[7,8] The 5-*endo-dig* electrophilic cyclization of 1,4-diarylbut-3-yn-1-ones (propargylic ketones, **1**) with NBS or NIS/acetone and iodine monochloride/dichloromethane, provided unsymmetrically 2,5-disubstituted 3-halofurans with excellent regiocontrol in high yields.^[9,10] Previously, this family of compounds was difficult to prepare efficiently since direct halogenation generally leads to mixtures of regioisomers.^[11] Given the lack of general methodology for analogous chloro adducts, we were interested in extending our work to monohalogenated β-chlorofurans, to provide a new methodology for accessing chloroheterocycles and new substrates for Suzuki–Miyaura coupling.

Results and Discussion

N-Chlorosuccinimide (NCS) gave no reaction, or negligible conversion, when mixed with butynone **1a** in toluene, dichloromethane, or acetone, at room temp. for over 20 h. When nucleophilic activation of NCS with phenylselenenyl chloride, as described by Mellegaard and Tunge,^[6] was investigated, slow formation of multiple products was observed. Thus, we turned our attention to another *N*-chloroimide, trichloro-*s*-triazinetriene (trichloroisocyanuric acid, TCCA),^[12] a more potent, though less selective and seldomly used, chlorination agent.

The potential of trichloro-*s*-triazinetriene as a substitute for chlorine in the halogenation of aromatic systems was

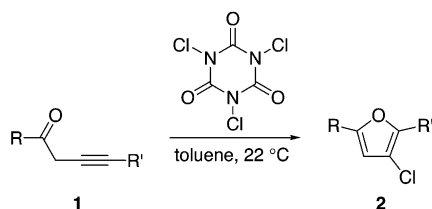
[a] Department of Chemistry, Oakland University, 2200 N. Squirrel Road, Rochester, Michigan 48309-4477, USA
E-mail: dembinski@oakland.edu

[b] Department of Chemistry, Eastern Illinois University, 600 Lincoln Avenue, Charleston, Illinois 61920-3099, USA

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

noted some time ago^[13] but did not elicit much interest.^[14] The few synthetic reports demonstrated the high chlorination potency that led to multiple chlorination products.^[15] In addition, the combined oxidation/chlorination reactivity hamper practical synthetic applications. There is industrial interest in TCCA owing to the high chlorine content (45.8% by weight). Nearly 100000 t/a of TCCA is produced and utilized in swimming pool maintenance or food processing, with relatively few applications in research laboratories.

Gratifyingly, we were able to find conditions for chlorocyclization of alkynones that lead to 2,5-disubstituted 3-chlorofurans. When ketones **1a–f**^[10a,16] were treated with TCCA in toluene by syringe pump addition, at room temperature, in the absence of base, nearly quantitative formation of **2a–f** was observed. Isolation by silica gel flash chromatography yielded new chlorofurans **2a–f** (Scheme 1, Table 1) that were characterized spectroscopically and gave excellent elemental analyses without further treatment.^[17] Finally, the production of **2a** in 87% yield was carried out using TCCA in the form of BioGuard, Smart Sticks which is marketed as swimming pool sanitizer.



Scheme 1. Preparation of chlorofurans **2** with the use of TCCA.

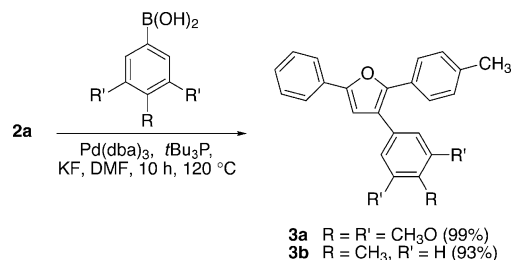
Table 1. Preparation of chlorofurans **2** with the use of TCCA.

Ynone	R	R'	Furan	Yield [%] ^[a]
1a	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	2a	94 ^[b]
1b	C ₆ H ₅	<i>c</i> -C ₃ H ₆	2b	79
1c	<i>p</i> -ClC ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	2c	92
1d	<i>p</i> -ClC ₆ H ₄	<i>p</i> - <i>t</i> BuC ₆ H ₄	2d	96
1e	<i>p</i> -BrC ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	2e	92
1f	<i>p</i> -BrC ₆ H ₄	<i>p</i> - <i>t</i> BuC ₆ H ₄	2f	95

[a] Reactions were carried out at room temp. on a 1.0 mmol scale with 0.4 mmol of TCCA dissolved in 8 mL of toluene (rate of addition 0.1–0.2 mL/min). [b] 87% with TCCA delivered as a pool sanitizer (BioGuard, Smart Sticks).

The TCCA reagent makes use of all three chlorine atoms, thus only requiring a 1:3 molar ratio. The precise stoichiometry needs to be controlled, as excess reagent leads to chlorination of both β positions producing 3,4-dichlorofurans. Although the reaction of TCCA with aromatic rings is known, chlorination of the phenyl substituents or toluene (solvent) has not been noticed.

The chlorofuran **2a** was validated as a substrate for the Suzuki–Miyaura coupling reaction using the catalytic system elaborated by Fu et al.^[18] in DMF (Scheme 2). 2,3,5-Triaryl-substituted furans **3a,b** were obtained in high yields (93–99%). Product **3a** was characterized by X-ray crystallography (Figure 1).^[19] The established conditions (120 °C, 10 h) are comparable to the coupling of β -iodofurans (90 °C, 24 h).^[9a]



Scheme 2. Suzuki–Miyaura coupling of chlorofuran **2a**.

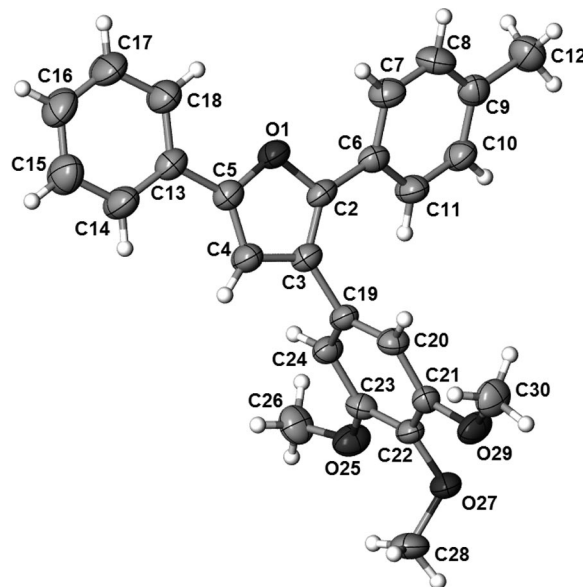
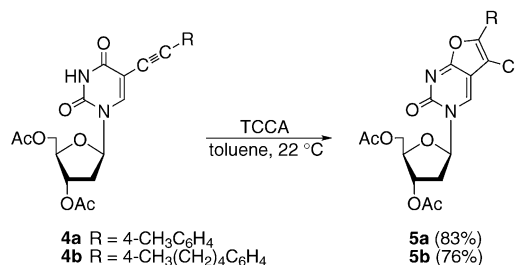


Figure 1. X-ray structure of furan **3a** (displacement parameters at the 50% probability level).

Europrymidine nucleosides are potent and selective antiviral agents with high specific activity against the varicella-zoster virus (VZV). Considering the importance of these bicyclic nucleosides, we decided to examine the use of TCCA for a cyclization of 5-alkynyl-2'-deoxyuridines **5**^[20] to produce chloro-substituted analogues. The furo-nucleosides containing 4-pentylphenyl and *p*-tolyl substituents belong to the group of the most effective structures with the 4-pentylphenyl compound being the most potent and selective anti-VZV agent reported.^[21]



Scheme 3. Synthesis of 5-chlorofuropyrimidine nucleosides **5**.

Acyl protection of the ribose hydroxy groups afforded greater solubility of the nucleosides in toluene. TCCA combined with the acetylated alkynyluridines **4a,b**^[22] gave 5-chlorofuropyrimidine nucleosides **5a,b** in 76–83% yield, analogously to the reactivity observed during the synthesis of the chlorofurans (Scheme 3).

Conclusions

We have demonstrated that TCCA is a highly efficient reagent for the quantitative chlorocyclization of but-3-yn-1-ones at room temperature and in the absence of a base. Other important features of this process are ease of product isolation and high yields. Relatively short reaction times and an easy to handle chlorination reagent (sold as a pool sanitizer) open new avenues to synthetically useful electrophilic reactions. Our approach allows for straightforward preparation of highly substituted furans. With efficient atom economy, this method facilitates the introduction of substituents that are not easily introduced by other methods.^[23] Determination of scope of the reaction with alkyl-only substituents is the subject of further investigation in our laboratory. These synthetic advances were also extended to the preparation of potent antiviral furopyrimidine nucleosides analogues from 5-alkynyl-2'-deoxyuridines.

Supporting Information (see also the footnote on the first page of this article): ¹H, ¹³C NMR spectra for **2**, **3**, and **5** (also HETCOR); X-ray table for **3a**.

Acknowledgments

We acknowledge the donors of the Petroleum Research Fund administered by the American Chemical Society (ACS-PRF#46094), the National Institute of Health (NIH) (CA111329), Oakland University and its Research Excellence Program in Biotechnology for support of this research. A. S. is grateful for the Provost's Graduate Student Research Award. We are thankful to Dr. W. E. Meyer (Chemtura) and Frontier Scientific, Inc., Logan, Utah, USA for a generous supply of BioGuard Smart Sticks and boronic acids, respectively.

- [1] Selected recent representative examples: a) A. S. Guram, X. Wang, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli, *J. Org. Chem.* **2007**, *72*, 5104–5112; b) A. S. Guram, A. O. King, J. G. Allen, X. Wang, L. B. Schenkel, J. Chan, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli, P. J. Reider, *Org. Lett.* **2006**, *8*, 1787–1789; c) B.-X. Tang, F. Wang, J.-H. Li, Y.-X. Xie, M. B. Zhang, *J. Org. Chem.* **2007**, *72*, 6294–6297.
- [2] For examples of coupling of β -chloro-substituted N-heterocycles, see: a) T. Ikawa, T. E. Barder, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007; b) N. Marion, P. de Frémont, I. M. Puijk, E. C. Ecarnot, D. Amoroso, A. Bell, S. P. Nolan, *Adv. Synth. Catal.* **2007**, *349*, 2380–2384.
- [3] Review: Larock, R. C. "Synthesis of Heterocycles and Carbocycles via Electrophilic Cyclization of Alkynes," in *Acetylene Chemistry – Chemistry, Biology, and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, New York, **2005**, vol. 2, pp. 51–99.
- [4] Citation of recent publications in the area exceeds the space limit of this article; selected recent examples: a) S. P. Bew, G. M. M. El-Taieb, S. Jones, D. W. Knight, W.-F. Tan, *Eur. J. Org. Chem.* **2007**, 5759–5770; b) J. P. Waldo, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 9643–9647; c) D. Alves, C. Luchese, C. W. Nogueira, G. Zeni, *J. Org. Chem.* **2007**, *72*, 6726–6734; d) J. Barluenga, H. Vázquez-Villa, I. Merino, A. Ballesteros, J. M. González, *Chem. Eur. J.* **2006**, *12*, 5790–5805; e) K. O. Hessian, B. L. Flynn, *Org. Lett.* **2006**, *8*, 243–246.
- [5] a) A.-Y. Peng, Y.-X. Ding, *Tetrahedron* **2005**, *61*, 10303–10308; b) H. Zhou, J. Yao, G. Liu, *Tetrahedron Lett.* **2008**, *49*, 226–228.
- [6] S. R. Mellegaard, J. A. Tunge, *J. Org. Chem.* **2004**, *69*, 8979–8981.
- [7] A. Sniady, K. A. Wheeler, R. Dembinski, *Org. Lett.* **2005**, *7*, 1769–1772.
- [8] M. S. Rao, N. Esho, C. Sergeant, R. Dembinski, *J. Org. Chem.* **2003**, *68*, 6788–6790.
- [9] For recent examples for the synthesis of 3-chlorofurans, see: a) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991–3000; b) A. S. Dudnik, A. W. Sromek, M. Rubina, J. T. Kim, A. V. Kel'in, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, *130*, 1440–1452.
- [10] For relevant, zinc chloride catalyzed cycloisomerizations, see: a) A. Sniady, A. Durham, M. S. Morreale, A. Marcinek, S. Szafert, T. Lis, K. R. Brzezinska, T. Iwasaki, T. Ohshima, K. Mashima, R. Dembinski, *J. Org. Chem.* **2008**, *73*, in press, DOI: 10.1021/jo8007995; b) A. Sniady, A. Durham, M. S. Morreale, K. A. Wheeler, R. Dembinski, *Org. Lett.* **2007**, *9*, 1175–1178.
- [11] C. W. Rees, T.-Y. Yue, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2247–2252.
- [12] G. A. Hiegel, "Trichloroisocyanuric Acid", in *The Electronic Encyclopedia of Reagents for Organic Synthesis*, <http://mrw.interscience.wiley.com/eros/>, DOI: 10.1002/047084289X.rt209.
- [13] E. C. Juenge, D. A. Beal, W. P. Duncan, *J. Org. Chem.* **1970**, *35*, 719–722.
- [14] Reviews: a) A. C. Cuhna, F. M. da Paixão, M. C. B. V. de Souza, V. F. Ferreira, *Quim. Nova* **2006**, *29*, 520–527, DOI: 10.1590/S0100-40422006000300021; b) J. C. Barros, *Synlett* **2005**, 2115–2116; c) U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 384–393.
- [15] a) G. F. Mendonça, R. R. Magalhães, M. C. S. de Mattos, P. M. Esteves, *J. Braz. Chem. Soc.* **2005**, *16*, 695–698; b) see also: R.-Y. Tang, P. Zhong, Q.-L. Lin, *J. Fluorine Chem.* **2007**, *128*, 636–640.
- [16] A. Sniady, M. S. Morreale, R. Dembinski, *Org. Synth.* **2007**, *84*, 199–208.
- [17] Representative procedure: **3-Chloro-2-(4-methylphenyl)-5-phenylfuran (2a)**: A round-bottom flask, equipped with a magnetic stir bar and a rubber septum was charged with 4-(4-methylphenyl)-1-phenylbut-3-yn-1-one (**1a**) (0.305 g, 1.30 mmol) and toluene (20 mL). A separate flask, equipped with a magnetic stir bar and a rubber septum was charged with TCCA (0.121 g, 0.520 mmol) and toluene (10 mL), and the resulting mixture was stirred until all of the TCCA had dissolved. Then the TCCA solution was drawn into a 10 mL syringe and dispensed into the reaction vessel with a syringe pump at a rate of 0.1–0.2 mL/min. When the addition was complete, the reaction mixture was stirred for an additional 1 h. The solvent was removed by rotary evaporation. Silica gel column chromatography (2.5 × 15 cm; CHCl₃) gave a colorless fraction. The solvent was removed by rotary evaporation, and the residue was dried by oil-pump vacuum to give **2a** as a white solid (0.329 g, 1.22 mmol, 94%), m.p. 58–59 °C.
- [18] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
- [19] CCDC-670297 (for **3a**) 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.

- [20] S. Meneni, I. Ott, C. D. Sergeant, A. Sniady, R. Gust, R. Dembinski, *Bioorg. Med. Chem.* **2007**, *15*, 3082–3088.
- [21] C. McGuigan, J. Balzarini, *Antiviral Res.* **2006**, *71*, 149–153.
- [22] For preparation, see: N. Esho, J.-P. Desaulniers, B. Davies, H. M.-P. Chui, M. S. Rao, C. S. Chow, S. Szafert, R. Dembinski, *Bioorg. Med. Chem.* **2005**, *13*, 1231–1238.
- [23] T. J. Donohoe, L. P. Fishlock, A. R. Lacy, P. A. Procopiou, *Org. Lett.* **2007**, *9*, 953–956.

Received: January 31, 2008

Published Online: May 30, 2008

Minor changes have been made to the article since its publication in Early View.