SYNLETT
Spotlight 470

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

2,4,6-Trichlorobenzoyl Chloride (Yamaguchi Reagent)

Compiled by Tharun Kumar Kotammagari

Tharun Kumar Kotammagari was born in Andhra Pradesh state, India. He received his M.Sc. degree in organic chemistry from Jawaharlal Nehru Technological University, Anantapur. He is currently working towards his Ph.D. degree at the Division of Organic Chemistry of CSIR-National Chemical Laboratory, Pune, India under the supervision of Dr. Asish K. Bhattacharya. His research is focused on the synthesis of bioactive natural products, isolation and structure elucidation of biologically active secondary metabolites and development of new synthetic methodologies.

Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, Maharashtra, India
E-mail: tk.kotammagari@ncl.res.in

Dedicated to my beloved parents and my research supervisor Dr. Asish K. Bhattacharya.

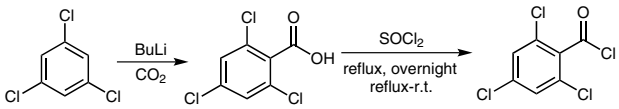
Introduction

2,4,6-Trichlorobenzoyl chloride (TCBC), known as Yamaguchi reagent, is widely used for the Yamaguchi esterification. Yamaguchi and co-workers were the first to discover its use as esterifying reagent in 1979.[1] It is a light yellow colored liquid (bp 107–108 °C, ρ = 1.561 g/cm^3)[2] and a moisture-sensitive reagent.

TCBC allows the regioselective synthesis of highly functionalized esters under mild reaction conditions. The Yamaguchi esterification is one of the most preferred protocol for macrolactonizations as evident by more than 340 research papers published using this methodology.[3]

Preparation

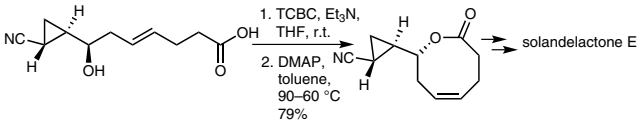
TCBC was first prepared by Yamaguchi and co-workers from 2,4,6-trichloroaniline.[4] Seebach and colleagues reported a simple synthesis from 1,3,5-trichlorobenzene (Scheme 1).[5]



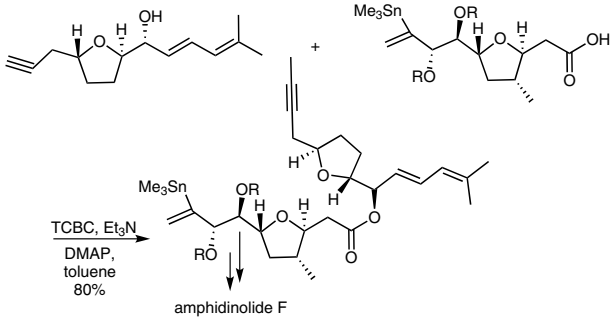
Scheme 1 Preparation of the Yamaguchi reagent

Abstracts

(A) *Asymmetric Total Synthesis of Solandelactone E:*
Solandelactone E, an eight-membered lactone, was isolated from the hydroid *Solanderia secunda*. Robinson and Aggarwal reported its synthesis through an intramolecular coupling of an acid and an alcohol using TCBC.[6]



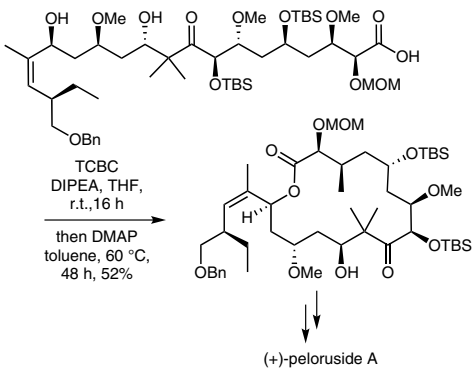
(B) *Total Synthesis of Amphidinolide F:*
The synthesis of amphidinolide F, a marine bioactive natural product was accomplished by Fürstner and co-workers by carrying out intermolecular esterification of acid and alcohol fragments utilizing TCBC to furnish the key intermediate which on further manipulation led to the target molecule.[7]



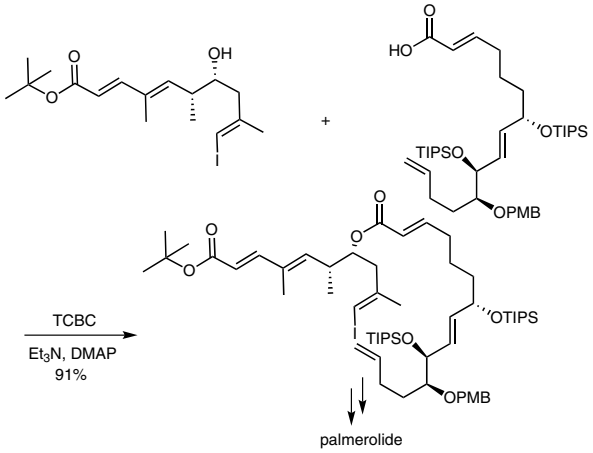
SYNLETT 2014, 25, 1335–1336
Advanced online publication: 28.04.2014
DOI: 10.1055/s-0033-1341245; Art ID: st-2014-v0477-v
© Georg Thieme Verlag Stuttgart · New York

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

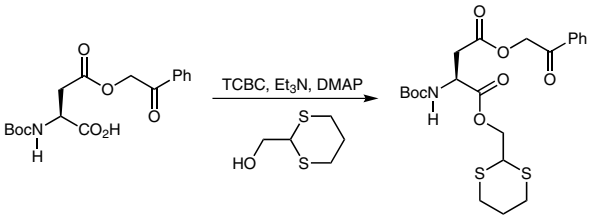
(C) *Synthesis of (+)-Peloruside A:*
(+)-Peloruside A, a sixteen-membered macrocyclic lactone was isolated by Northcote and co-workers from a marine sponge of the Pelorus Sound in New Zealand. Its synthesis was carried out by Jacobsen and co-workers by intramolecular esterification using TCBC.[8]



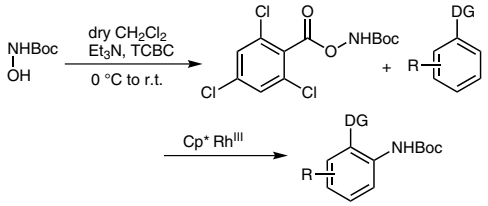
(D) *Synthesis of Palmerolide A:*
Palmerolide A, a cytotoxic macrolide was isolated from the Antarctic tunicate *Synoicum adareanum*. Recently, Dudley and colleagues synthesized a twenty-membered lactone palmerolide A by coupling acid and alcohol subunits.[9]



(E) *Lack of Racemization of Stereocenters:*
The Yamaguchi esterification is often used in preference to other esterification methods due to its lack of racemization of stereocenters. Waldmann and Kunz reported that the Yamaguchi esterification yields the non-racemized product in the esterification of *N*-Boc-protected aspartate, whereas other methods racemize the chiral center.[10]



(F) Although TCBC is widely used in the Yamaguchi esterification, it has also been used as a protecting group for amines and alcohols. Glorius and co-workers reported the rhodium(III)-catalyzed amidation of C(sp^2)–H bonds by the use of electron-deficient aryloxycarbamates as efficient electrophilic amidation partners.[11] TCBC was used for the protection of the alcohol group in *tert*-butyl hydroxycarbamate.



References

(1) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(b) Kawanami, Y.; Dainobu, Y.; Inanaga, J.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 943.
(2) Ewin R. A., Pertusati F. **2013**. 2,4,6-Trichlorobenzoyl Chloride. e-EROS Encyclopedia of Reagents for Organic Synthesis.
(3) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. *Chem. Rev.* **2013**, *113*, PR1.
(4) Inanaga, J.; Katsuki, T.; Takimoto, S.; Ouchida, S.; Inoue, K.; Nakano, A.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1021.
(5) Sutter, M. A.; Seebach, D. *Liebigs Ann. Chem.* **1983**, 939.
(6) Robinson, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 6673.
(7) Valot, G.; Regens, C. S.; O'Malley, D. P.; Godineau, E.; Takikawa, H.; Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9534.
(8) McGowan, M. A.; Stevenson, C. P.; Schiffler, M. A.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 6147.
(9) Lisboa, M. P.; Jones, D. M.; Dudley, G. B. *Org. Lett.* **2013**, *15*, 886.
(10) Waldmann, H.; Kunz, H. *J. Org. Chem.* **1988**, *53*, 4172.
(11) Glorius, F.; Grohmann, C.; Wang, H. *Org. Lett.* **2013**, *15*, 3014.

 © Georg Thieme Verlag Stuttgart · New York

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.