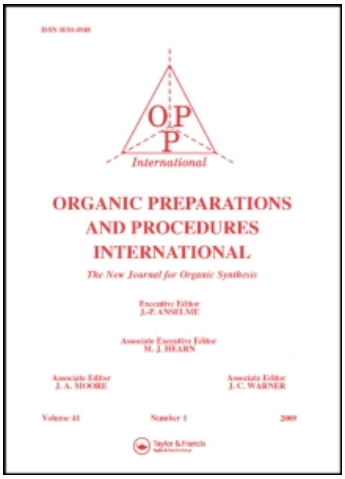


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

RECENT ADVANCES IN THE CHEMISTRY OF TRICHLOROMETHYL CHLOROFORMATE AND *bis*-(TRICHLOROMETHYL) CARBONATE

Weike Su[a]; Weihui Zhong[a]; Gaofeng Bian[a]; Xiangjun Shi[a]; Jianping Zhang[a]
[a] College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, P. R., CHINA

To cite this Article Su, Weike , Zhong, Weihui , Bian, Gaofeng , Shi, Xiangjun and Zhang, Jianping(2004) 'RECENT ADVANCES IN THE CHEMISTRY OF TRICHLOROMETHYL CHLOROFORMATE AND *bis*-(TRICHLOROMETHYL) CARBONATE', Organic Preparations and Procedures International, 36: 6, 499 — 547
To link to this Article: DOI: 10.1080/00304940409355972
URL: http://dx.doi.org/10.1080/00304940409355972

ORGANIC PREPARATIONS AND PROCEDURES INT., 36 (6), 499-547 (2004)

RECENT ADVANCES IN THE CHEMISTRY OF TRICHLOROMETHYL CHLOROFORMATE AND *bis*-(TRICHLOROMETHYL) CARBONATE

Weike Su*, Weihui Zhong, Gaofeng Bian, Xiangjun Shi and Jianping Zhang

College of Pharmaceutical Sciences, Zhejiang University of Technology
Hangzhou, 310014, P. R. CHINA
e-mail: suweike@zjut.edu.cn Tel & Fax: +86-571-88320752

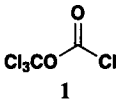
RECENT ADVANCES IN THE CHEMISTRY OF TRICHLOROMETHYL CHLOROFORMATE AND *bis*-(TRICHLOROMETHYL) CARBONATE

Weike Su*, Weihui Zhong, Gaofeng Bian, Xiangjun Shi and Jianping Zhang

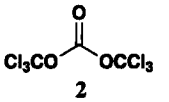
College of Pharmaceutical Sciences, Zhejiang University of Technology
Hangzhou, 310014, P. R. CHINA
e-mail: suweike@zjut.edu.cn Tel & Fax: +86-571-88320752

INTRODUCTION

Trichloromethyl chloroformate (**TCF**, diphosgene, **1**) and *bis*-(trichloromethyl) carbonate (**BTC**, triphosgene, **2**), two important substitutes for phosgene,[1-9] have emerged as versatile synthetic auxiliaries for the synthesis of important classes of organic compounds. Recently, for example, a large number of compounds with high biological activities have been synthesized by use of **TCF** and **BTC**. The present review presents a summary on the recent development of **TCF** and **BTC**.



1
(**TCF**, diphosgene)



2
(**BTC**, triphosgene)

Scheme 1

It is well known that phosgene has long been of tremendous importance in organic chemistry for a wide variety of synthetic applications.[2] However, it has several disadvantages: First, being a gas makes it difficult to measure accurately the amount used and to avoid side-reactions when an excess is used. Second, it is a highly toxic gas, which makes its use and trans-portation severely restricted. Now its use has been banned in both research labs and industrial plants. In contrast, **TCF** is a colorless liquid and **BTC** is a crystalline solid. Both are soluble in solvents such as ether and chloroform. The most important properties of **TCF** and **BTC** are shown in *Table 1*.

Table1. Some Physicohemical Properties of Phosgene, **TCF** and **BTC**

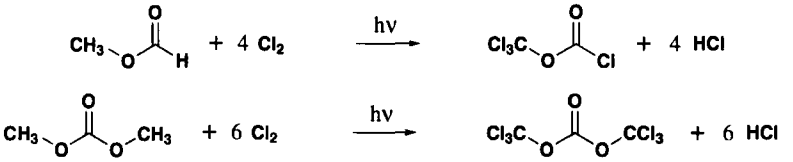
Properties	Phosgene	TCF	BTC
Appearance	Colorless gas	Colorless liquid	White crystal
Molecular formula	CCl_2O	$C_2Cl_4O_2$	$C_3Cl_6O_3$
Molecular weight	98.92	197.85	296.75
bp.℃	8	128	203-206
mp.℃	–118	–57	81-83
Density	1.38	1.65	1.73
Vapor pressure (mmHg/20℃)	1215	10	----[a]

[a]It decomposes above 90℃ in moist air.

TCF may be prepared by illumination of methyl formate and chlorine with a 500-watt lamp[3] **BTC** can be obtained by Councler's route[4a] or Eckert's method[4b] or by UV irradiation of dimethyl carbonate and chlorine[5].

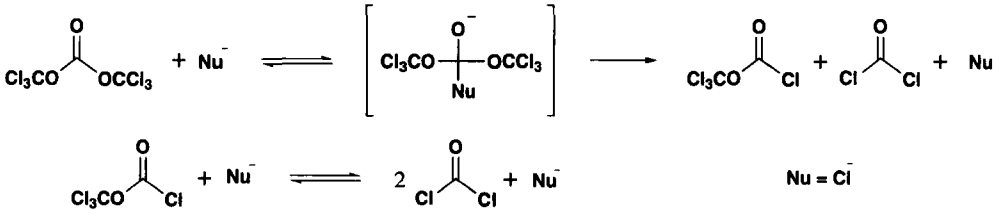
bis-(Trichloromethyl) Carbonate.-*[4b] Chlorine gas was bubbled into a stirred solution of dimethyl carbonate (45.0 g, 0.3 mol) in 250 mL of carbon tetrachloride, cooled to 10-20°C and irradiated with two lamps (Philips MLU 300W) for 28 hrs of net reaction (it is possible to interrupt the reaction). The reaction was monitored by ^1H NMR. Removal of the solvent in vacuo (200 Torr) gave a crystalline solid which, after drying in vacuo at 0.1 Torr, afforded 143.0 g, (97%) of a white solid, mp. 79°C. The HCl gas evolved was trapped into 1.6 L of a 20% aqueous sodium carbonate solution.*

TCF may be synthesized from methyl formate by a similar procedure (*Scheme 2*).[3]



Scheme 2

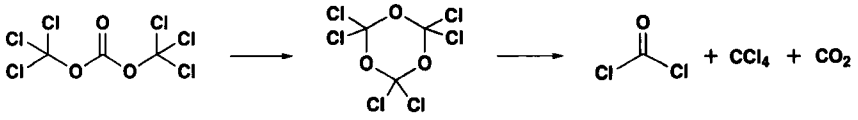
TCF and **BTC** are valuable, cost-effective substitutes for phosgene. The main reason is that they can be handled more safely and more easily than phosgene.[6] Pasquato[7] proposed a mechanism, shown in *Scheme 3*, for the mode of action of **TCF** and **BTC**. It was found that one



Scheme 3

equivalent of **TCF** can produce two equivalents of phosgene, while **BTC** can lead to three equivalents of phosgene thus making **TCF** and **BTC** safe synthetic equivalents of phosgene.

Pulay[8] has pointed out that **BTC** may be converted to phosgene *via* a six-membered ring intermediate (*Scheme 4*).



Scheme 4

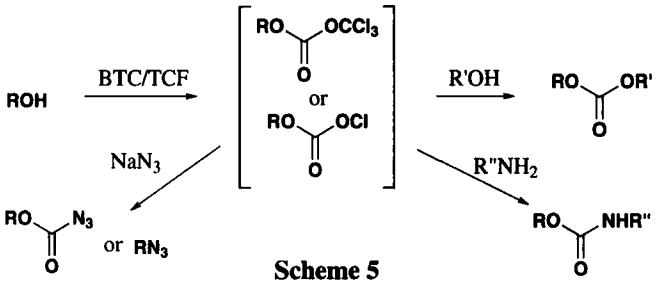
Table 2 provides a comparison of the reactivity of phosgene and its substitutes.[7] It has been reported that the reactivity of phosgene is 18.7 times greater than that of **TCF** and 170 times that of **BTC**. Therefore, the reactions of both substitutes may be controlled more easily than those of phosgene.

Table 2. Relative Reactivity in Pseudo First-order Reactions with 30 Equivalents of Methanol at 25°C in $CDCl_3$

	Phosgene	TCF	BTC
Relative reactivity	170	9.1	1

I. REACTIONS WITH ALCOHOLS AND THIOLS

Treatment of alcohols with **BTC** or **TCF** gives chloroformates or (trichloromethoxy) formates very readily. However, most of these compounds are unstable and difficult to isolate. They are usually used in the subsequent reactions without further purification. Treatment of these species with alcohols, amines and azide ion provides a convenient access to carbonates, carbamates and azidoformates respectively (*Scheme 5*).



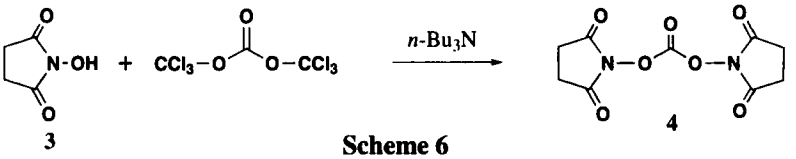
Scheme 5

1. Preparation of Carbonates

a. Preparation of Symmetrical Carbonates

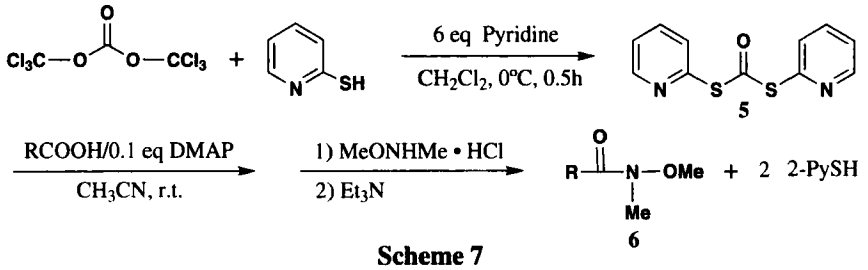
BTC and **TCF** are convenient reagents for the introduction of the carbonate moiety. Symmetrical carbonates are well-known compounds and synthetic difficulties are not expected.[1] They have been used as coupling agents such as *N,N*-disuccinimidyl carbonate (DSC, **4**) and *S,S*-

di(2-pyridyl)dithiocarbonate (**5**). DSC may be utilized in many synthetic applications because of its stability. A high-yield, improved method for a large scale preparation of DSC from **BTC** and *N*-hydroxysuccinimide **3** involving a simple work-up, has been developed. (*Scheme 6*).[10]



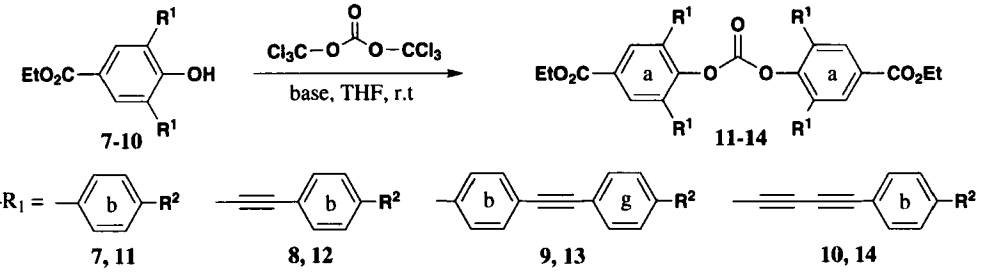
Scheme 6

S,S-*bis*-(2-Pyridyl)dithiocarbonate (**5**) was prepared by addition of six equivalents of 2-mercaptopyridine and pyridine in dichloromethane to **BTC** at 0°C.[11] *N*-Methoxy-*N*-methylamides **6**, which are effective acylating agents because of their reaction with organometallics to produce ketones without side-products,[1] can be conveniently prepared from carboxylic acids and *N,O*-dimethylhydroxylamine hydrochloride, using **5** as the coupling agent in a one-pot reaction (*Scheme 7*).



Scheme 7

Diphenyl carbonate can be used as a covalent template in the synthesis of a [2]-catenane.[13] Recently, Godt and Unsal[14] found that the use of different bases (pyridine, DMAP, NaH) had a strong influence on the conversion in the preparation of diaryl carbonates. Carbonates **11** and **12** could be prepared from the corresponding phenols **7** or **8** and BTC using pyridine as the base (*Scheme 8*). However, in the case of carbonates **13** and **14**, NaH was preferable.



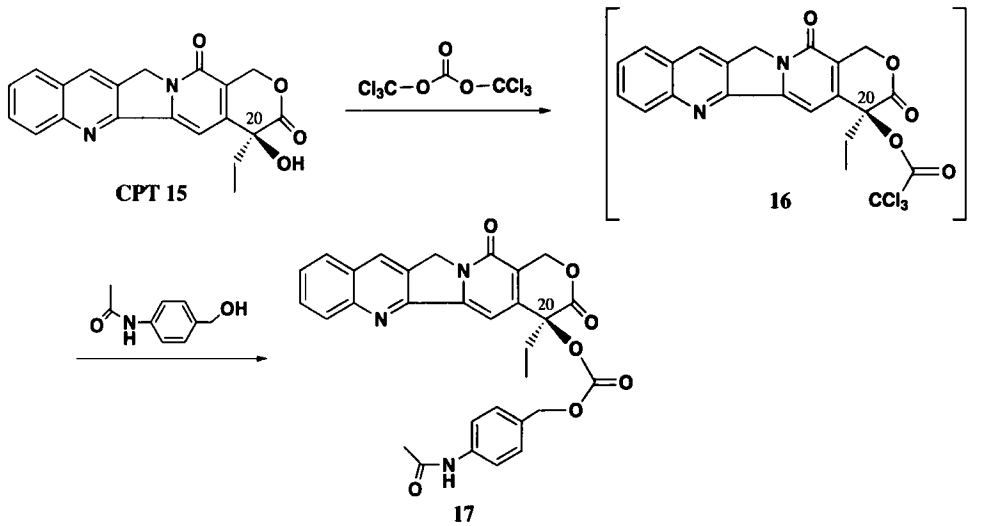
Scheme 8

Rotaxanes are of current interest as model systems for molecular recognition and as precursors for molecular devices. The rotaxane with a carbonate axle could be formed from the reaction between **TCF** and wheeled phenolate blocking groups.[15]

N,N-Disuccinimidyl Carbonate (DSC). Typical Procedure.-[10] *The reaction was carried out in an inert atmosphere. N-Hydroxysuccinimide (805 g, 7 mol) and triphosgene (417 g, 1.4 mol) were dissolved in THF (6 L), and cooled in an ice bath. Then a solution of tri-n-butylamine (1567.6 g, 8.43 mol) in THF (2 L) was added dropwise at a rate such that the reaction temperature was maintained in the range 0-5°C; a precipitate formed. After the addition was complete, the reaction was stirred at room temperature for 12-16 h. The resulting slurry was cooled in an ice bath for 30 min, and then the solid was collected by filtration. The filter cake was washed with cold THF (2 x 500 mL) and dried under vacuum to afford 796.5 g of DSC (89% yield), mp. 218-220°C.*

b. Preparation of Unsymmetrical Carbonates

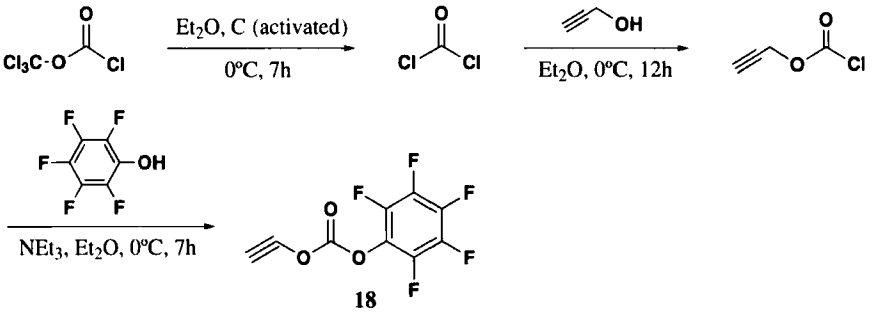
Carbonate linkages have very wide applications in chemistry, such as, for example, in the design and synthesis of pro-drugs, peptide and protein, chemiluminescence assays, and underfill technology. Through this concept, pro-drugs, synthesized *via* carbonate linkages by reaction of the parent drug with carbonate activated the pro-moiety, usually can improve the stability and the water-solubility of the drug. **BTC** and **TCF** are two convenient reagents for the synthesis of such carbonate activated pro-moieties. A model pro-drug of the camptothecins (CPTs, **17**) linked with a carbonate function to the 20-hydroxy group was obtained by reaction of CPT-20-chloroformate **16** with a model alcohol (Ac-PABA).[16] CPT **15** was activated with **BTC** in the presence of a base to generate the highly reactive intermediate chloroformate **16** *in situ* (*Scheme 9*).



Scheme 9

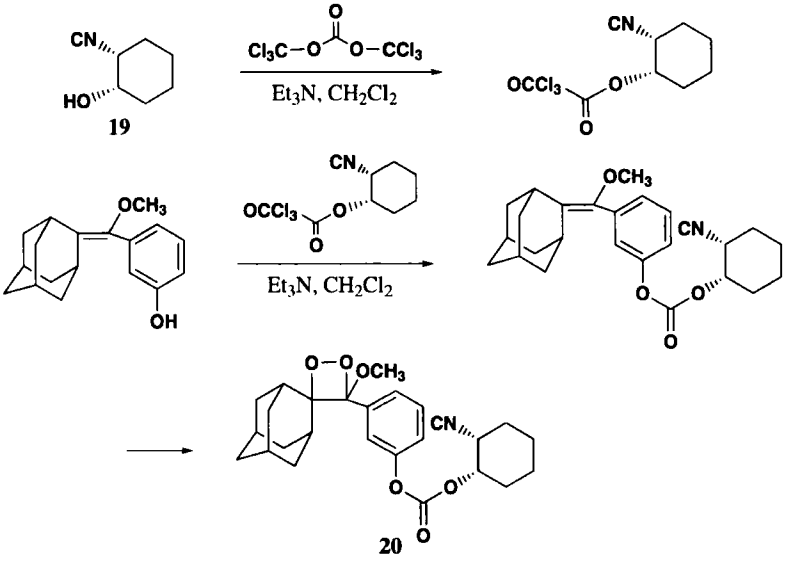
Propargyl pentafluorophenylcarbonate (Poc-Opfp, **18**)[17] is a novel reagent used for the preparation of *N-Poc* amino acids and peptides in excellent yields, and is better than Fmoc-OPfp in terms of thermal stability and reactivity. The reagent (Poc-Opfp, **18**) can be easily synthesized

under mild conditions by treatment of propargyl alcohol and **TCF**, followed by the addition of pentafluorophenol (*Scheme 10*).



Scheme 10

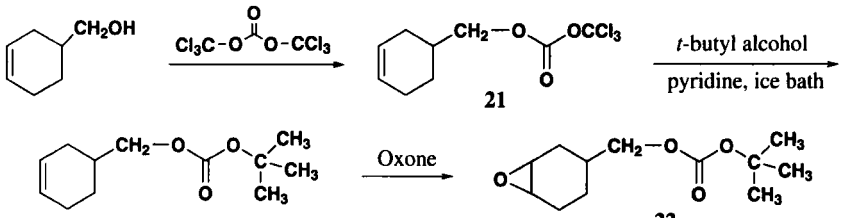
Chemiluminescence assays have recently attracted much attention as an analytical method in the field of clinical and biochemical studies because of their high sensitivity, simplicity, and safety.[18] A new chemiluminescent triggerable 1,2-dioxetane **20** has been synthesized *via* the key intermediate chloroformate derived from **BTC** and *cis*-2-hydroxycyclohexanecarbonitrile **19**, by use of *cis*-2-cyanocyclohexyl carbonate as a protective group, as shown in *Scheme 11*.[19]



Scheme 11

In order to develop thermally reworkable underfills that can provide good reliabilty to the flip-chip package and allow the chip to be removed easily at elevated temperatures, Wang and Li[20] reported the synthesis of several cyclic epoxides containing thermally cleavable carbonate linkages. These authors found that carbonates with primary or secondary aliphatic

groups on both sides are easy to prepare by using **BTC**, but a carbonate containing tertiary aliphatic groups is much more difficult to prepare. 3,4-Epoxycyclohexylmethyl *t*-butyl carbonate (**22**) is a carbonate with a *t*-butyl group, which was obtained from 3-cyclohexenyl-1-methyl chloroformate (**21**) and *t*-butyl alcohol (*Scheme 12*). Terpineol and 2-(3-cyclohexenyl)-2-propanol



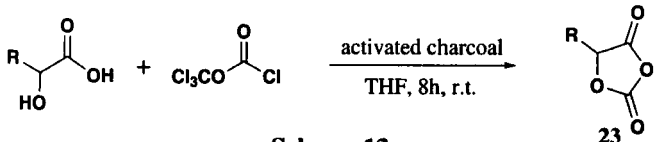
Scheme 12

were also used to react with 3-cyclohexenyl-1-methyl chloroformate under the same conditions; however, no analogous products were detected. Instead, 3-cyclohexenyl-1-methyl chloride was generated. A possible rationale is that steric hindrance prevents the formation of the anticipated tertiary carbonates.

Cyclohex-3-enylmethyl t-Butyl Carbonate. Typical Procedure.[20] *To a solution of triphosgene (4.40 g, 14.8 mmol) in a dichloromethane solution (50 mL) and cooled in a ice bath, was slowly added a solution of 3-cyclohexene-1-methanol (4.6 mL, 39.4 mmol) and pyridine (8 mL) in dichloromethane (50 mL) within 1 h. Then, the mixture was stirred for an additional 4 h in the ice bath to generate 3-cyclohexene-1-methyl chloroformate. To this mixture, a solution of 2-methyl-2-propanol (3.0 mL, 31.4 mmol) and pyridine (8 mL) in dichloromethane (50 mL) was then added in one portion. The mixture was then stirred at room temperature overnight. It was washed with a 0.5 N HCl solution (100 mL), 5% sodium bisulfite (500 mL), and 2.5% sodium bicarbonate (500 mL) and dried over magnesium sulfate. The organic phase was then concentrated and the residue obtained was purified by column chromatography on silica gel with dichloromethane to yield 3.93 g (47%) of the product as a colorless liquid.*

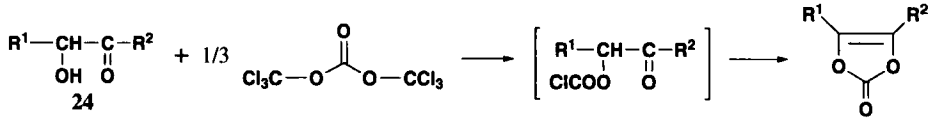
c. Preparation of Cyclic Carbonates

Both **BTC** and **TCF** are two highly efficient reagents for formation of cyclic carbonates. 1,3-Dioxolane-2,4-diones **23** are cyclic anhydrides which generate optically active α-hydroxy acids used in highly enantioselective ring-opening alcoholyses. An improved method for their preparation is the condensation of α-hydroxy acids with **TCF** in the presence of activated charcoal (*Scheme 13*).[21]



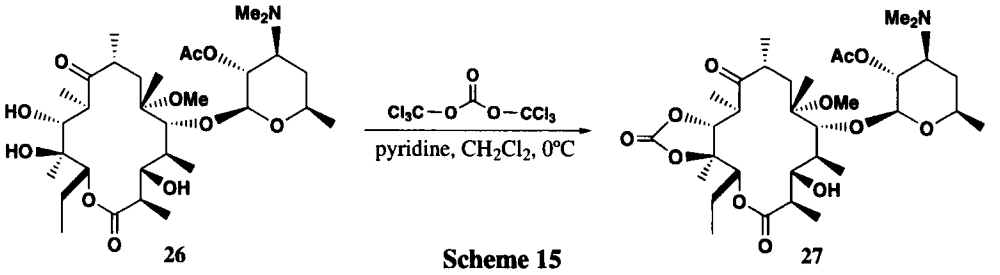
Scheme 13

4,5-Disubstituted-2-oxo-1,3-dioxolenes **25** have been employed as amino protecting group for amino acids during peptide synthesis and as dienophiles or dipolarophiles in cycloaddition reactions. Moreover, they have been used in the manufacture of *lenampicillin hydrochloride*, a pro-drug of *ampicillin*., both of which could be synthesized by cyclocarbonylation of appropriate a-hydroxyketones **24** with **BTC** in the presence of a base (*Scheme 14*).[22]



Scheme 14

The introduction of a cyclic carbonate at the 11,12-position of 2'-O-acetyl-5-O-desosaminyl-6-O-methylerythronolide A (**26**) enhanced the antibacterial activity of this macrolide antibiotic. Formation of the 11,12-carbonate **27** was carried out with **TCF** in a mixture of CH_2Cl_2 and pyridine (*Scheme 15*).[23]

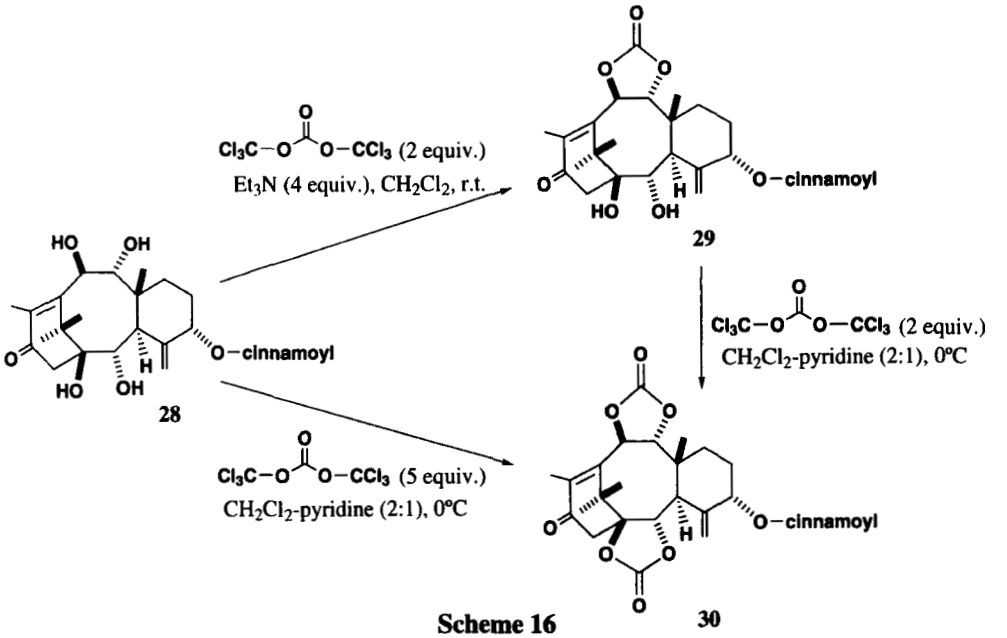


Scheme 15

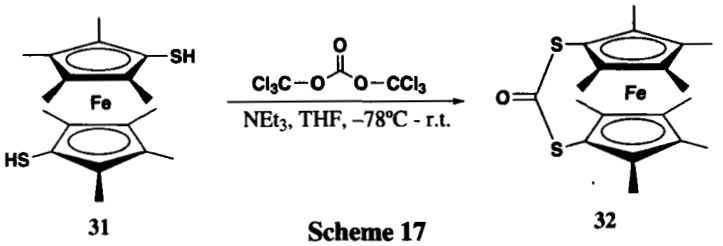
In the course of the synthesis of new 7-deoxypaclitaxel analogues for potential anti-cancer therapy,[24] attempted protection of the polyalcohol **28** with **BTC** in the presence of Et_3N yielded 9,10-cyclic carbonate alcohol **29** as the sole product in high yield. Furthermore, treatment of compound **29** with **BTC** in CH_2Cl_2-pyridine led to a 1:2, 9:10-dicyclic carbonate **30**; the latter product could also be prepared directly in 86% yield from the polyalcohol **28** under similar conditions using five equivalents of **BTC** (*Scheme 16*).

In another example, treatment of the octamethyl-ferrocene-dithiol **31** with **BTC** in the presence of Et_3N afforded the dithiacarbonyl ferrocenophane **32** in 70% yield (*Scheme 17*).[25]

Polycyclic carbonates, prepared by reaction of *novolac*-based phenol-formaldehyde resins with **BTC**, have been reported as curing agents for polycarbonate resins by cation-catalyzed transesterification.[26] Calixarenes are cyclic oligomers that demonstrate outstanding inclusion properties and have the capability of forming complexes with a number of metal cations, organic ion species, and large aromatic compounds such as C_{60}. Lower-rim bridging (linkage between hydroxy groups) has enabled the introduction of a seconf macrocyclophane into the parent calixarenes. A wide variety of lower-rim bridged calixarenes have also extended



Scheme 16

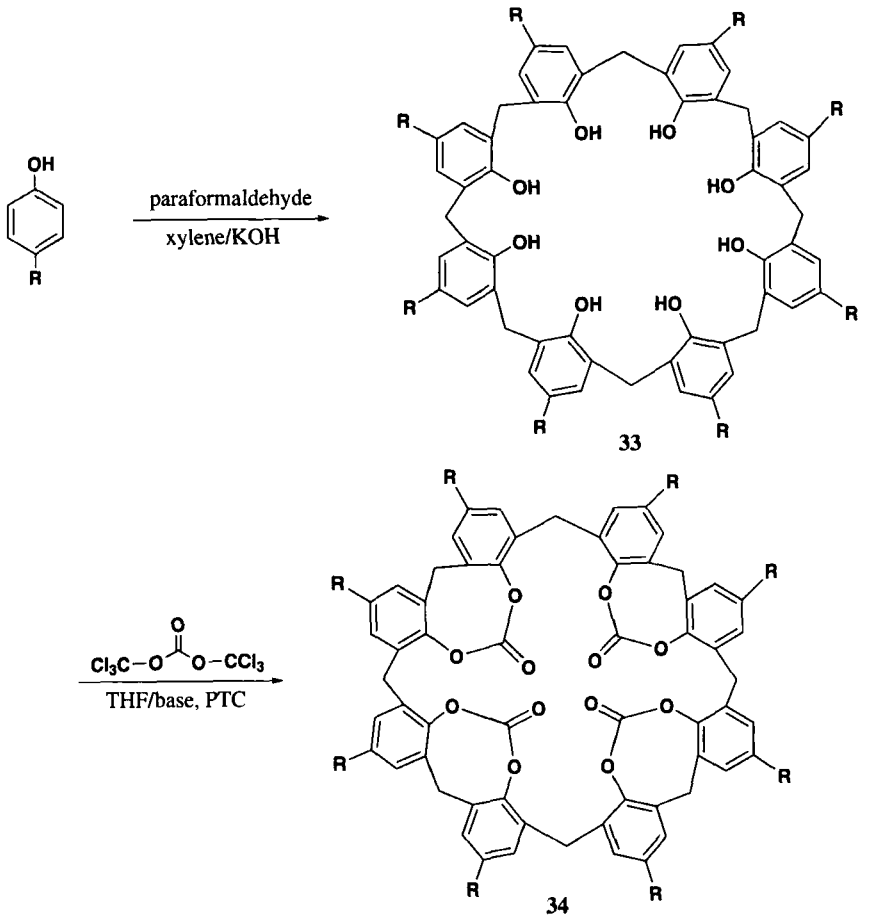


31 32

Scheme 17

the application of calixarenes. Sugioka and Hay[27] reported the synthesis of novel full lower-rim-bridged calix[8]arenes **34** with carbonate linkages *via* the condens*ation* of *p*-alkyl substituted calix[8]arenes **33** with BTC at 50°C (*Scheme 18*).

4,5-Dialkyl-2-oxo-1,3-dioxolenes: Typical Procedure.-[22] *To a stirred mixture of the α-hydroxyketone (10.0 mmol) and N,N-dimethylaniline (15.0 mmol) in dichloromethane (30 mL) was added dropwise a solution of* ***BTC*** *(7.5 mmol) in dichloromethane (10 mL) over a period of 1/2 hr at 0°C. The resulting solution was stirred at ambient temperature for 2 h. The solvent was distilled off and the resulting oily residue was heated in an oil bath at 160°C for 4 h. The oily product was distilled under vacuum or recrystallized to afford the 4,5-dialkyl-2-oxo-1,3-dioxolene in 47-67% yield.*

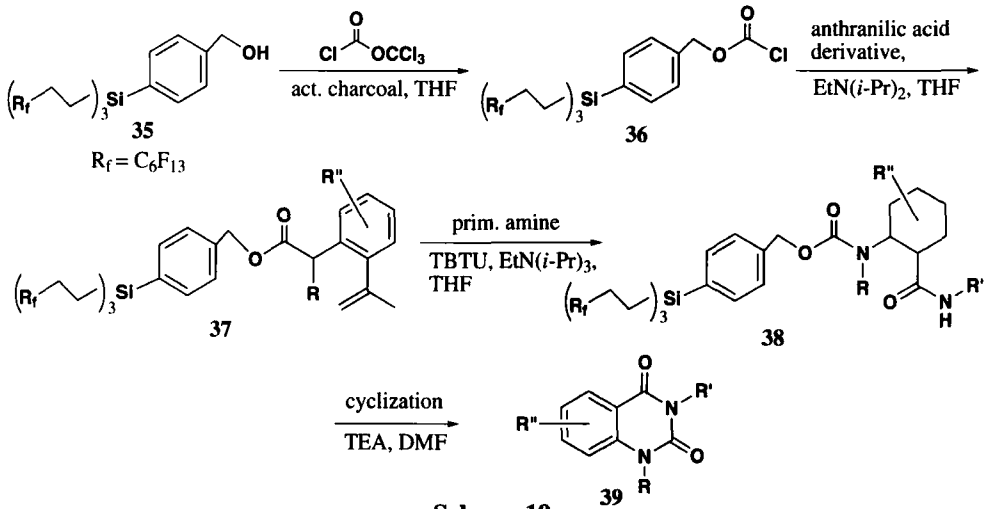


Scheme 18

2. Preparation of Carbamates

Carbamates are usually formed in one-pot reaction by treatment of alcohols with **TCF** or **BTC** to give chloroformates as the intermediates, followed by the addition of amines. This sequence of reactions has a wide application in organic synthesis.

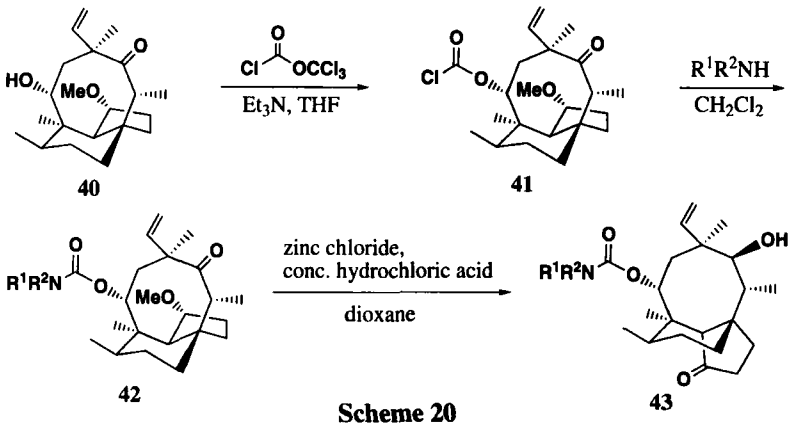
Quinazoline-2,4-diones (**39**) represent a group of attractive pharmacophores with a wide range of pharmacological activities. They could be prepared using a *perfluoro*-tagged protecting group, such as benzyl alcohol **35**.[28] For the coupling and benzyloxycarbonyl protection of anthranilic acids, the *perfluoro*-tagged benzyl alcohol was first treated with **TCF** to yield chloroformate **36**, followed by the addition of anthranilic acid derivatives to afford carbamates **37**. Then, a primary amine was coupled to the carboxylic acid function of the carbamates to yield amides **38**. The final cyclization step by means of intramolecular carbamate cleavage was initiated by Et_3N to yield quinazoline-2,4-diones **39** (*Scheme 19*).



35 $R_f = C_6F_{13}$ 36 37 38 39

Scheme 19

A novel series of mutilin 14-carbamates were found to have potent antibacterial activity, displaying a spectrum of activity that encompasses the major respiratory tract pathogens. The C_{14}-carbamate derivatives were prepared by a three-step process.[29] Treatment of 4-epi-mutilin **40** with **TCF** affords the corresponding chloroformate derivatives **41** which upon reaction with primary or secondary amines leads to a variety of 4-epi-mutilin 14-carbamate derivatives **42** in high yields. Once more, strong acid treatment effects rearrangement of the 4-epi-mutilin 14-carbamates to the corresponding mutilin derivatives **43** (*Scheme 20*).

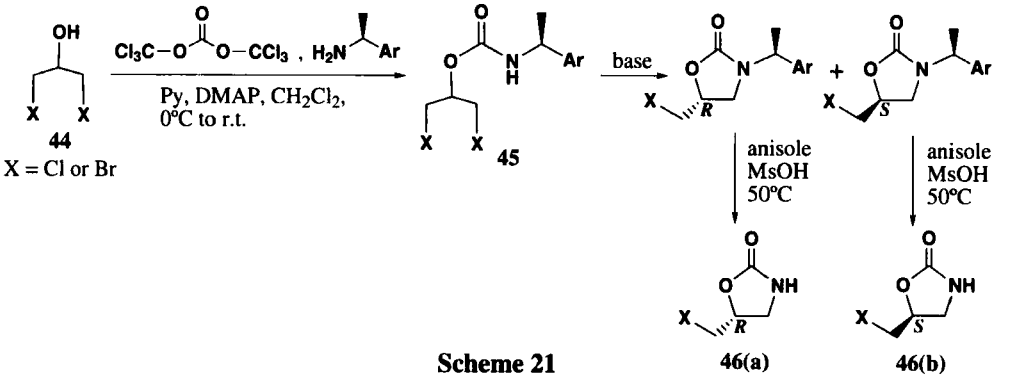


40 41 42 43

Scheme 20

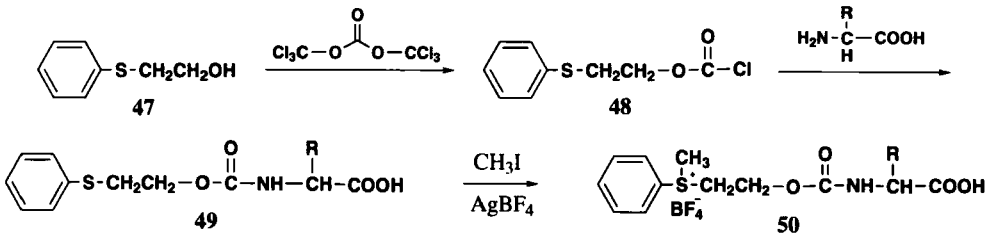
5-Halomethyl-2-oxazolidinones and their derivatives are useful chiral building blocks for organic synthesis. Optically active 5-halomethyl-2-oxazolidinones **46** were readily prepared from prochiral 1,3-dihalo-2-propanols **44** by a three-step sequence involving formation of carbamates **45** followed by asymmetric desymmetrization and debenzylation with an anisole-methanesulfonic acid system.[30] In the three-step procedure, the prochiral alcohols, 1,3-dibromo-2-

propanol and 1,3-dichloro-2-propanol, reacted with **BTC** in methylene chloride in the presence of pyridine and DMAP to give the carbamates in good yields (*Scheme 21*).



Scheme 21

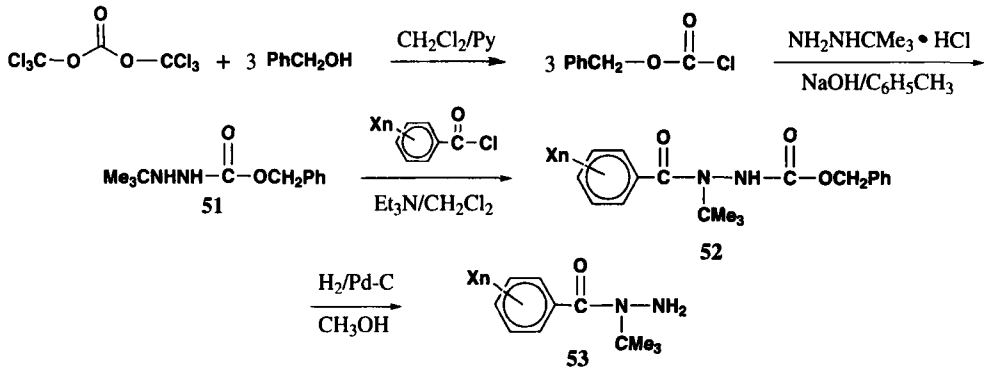
In order to perform solid-phase peptide synthesis in water, the 2-[phenyl(methyl)-sulfonio]ethoxycarbonyl tetrafluoroborate (Pms) group, a new water-soluble *N*-protecting group with high base lability and high polarity, has been developed.[31] Treatment of 2-(phenylthio)ethanol (**47**) and **TCF** in CH_2Cl_2, 2-(phenylthio)ethyl chloroformate **48** was formed. The chloroformate was then treated with an amino acid to give 2-[phenyl(methyl)sulfonio]ethoxy-carbonyl (Pte) amino acid **49**. After the addition of methyl iodide and silver tetrafluoroborate, Pms-amino acid **50** was obtained by the solid-phase method in water (*Scheme 22*).



Scheme 22

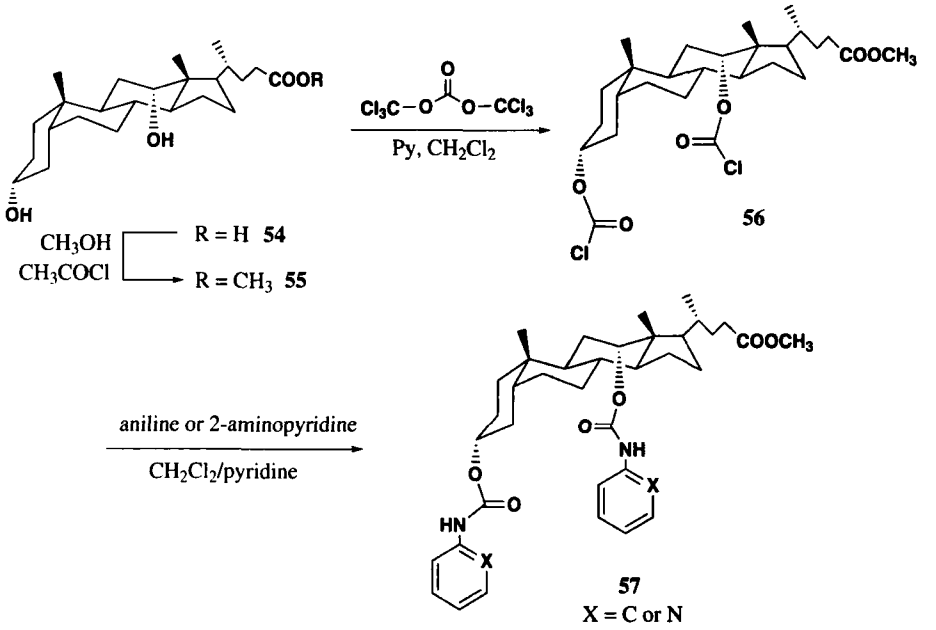
Recently, a new class of insect growth regulators (IGR), the *N-tert*-butyl-*N,N'*-diacyl-hydrazines (BDAH), have been found to mimic the action of 20-hydroxyecdysone in activating the ecdysone receptor leading to lethal premature molting. The relationship between the structure and biological activity of the *N-tert*-butyl-*N,N'*-dibenzoylhydrazine larvicides indicated *N-tert*-butyl-*N*-benzoylhydrazine is the biologically active unit. A series of novel *N'-tert*-butyl-*N'*-substituted benzoyl-*N*-(aryl)aminocarbonylhydrazines and their derivatives were synthesized and exhibited good larvicidal activities.[32] Benzyl chloroformate was synthesized by the reaction of benzyl alcohol and **BTC** in good yield for the first time and was condensed with *tert*-butylhydrazine hydrochloride to give *N-tert*-butyl-*N'*-benzyloxycarbonylhydrazine (**51**), and subsequent acylation with substituted benzoyl chlorides yielded the *N-tert*-butyl-*N'*-benzyloxycarbonyl-*N*-

substituted benzoylhydrazines **52**. Further deprotection using 5% Pd-C as a catalyst provided *N-tert*-butyl-*N*-substituted benzoylhydrazines **53** in good yields (*Scheme 23*).



Scheme 23

Molecular tweezers are novel artificial receptors, which have the advantage of efficient construction; in addition, their surfaces can be tailored for specific applications. A series of new chiral molecular tweezers has been synthesized by using deoxycholic acid as spacer and aromatic amines as arms.[33] Instead of using toxic phosgene, **BTC** was employed to bridge the 3a,12a-hydroxy groups in deoxycholic acid with aromatic amines. Deoxycholic acid **54** was first converted to methyl deoxycholate **55**. The latter was treated with **BTC** to give *bis*-chloroformate **56**, which reacted directly with different aromatic amines to yield molecular tweezers **57** (*Scheme 24*). These chiral molecular tweezers showed good enantioselectivity for D-amino acid methyl esters.



Scheme 24

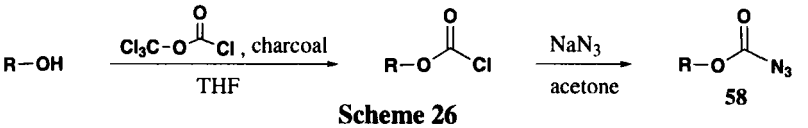
1,3-Dibromo-2-propyl (S)-N-(1-phenylethyl)carbamate. Typical Procedure.-[30] *Pyridine (4.80 g, 60.0 mmol) was added dropwise to a mixture of 1,3-dibromo-2-propanol (4.40 g, 20.2 mmol) and triphosgene (2 g, 6.74 mmol) in methylene chloride (50 mL) at 0°C. After being stirred for 2 h at rt, the mixture was cooled to 0°C, and (S)-(−)-1-phenylethylamine (2.45 g, 20.2 mmol), pyridine (1.60 g, 20.0 mmol) and a catalytic amount of DMAP (74 mg, 0.61 mmol) were added. The resulting mixture was stirred overnight at rt. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted with ether. The organic extracts were combined, washed once with water and once with saturated aqueous sodium chloride, dried with magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (hexane: ethyl acetate = 12:1) to give the 1,3-dibromo-2-propyl(S)-N-(1-phenylethyl)carbamate as a white solid (5.61 g, 76%).*

3. Preparation of Azides

a. Preparation of Azidoformates

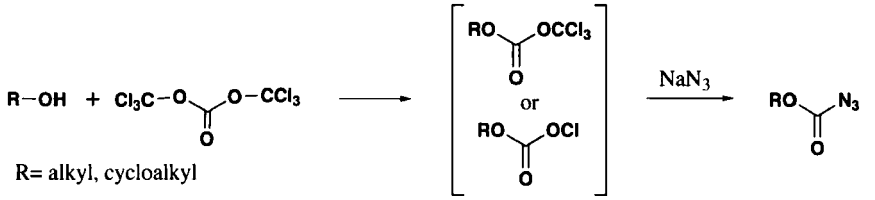
An efficient preparation of various azidoformates using **BTC** or **TCF** from alcohols and sodium azide has been developed. Azidoformates can be used efficient reagents for the protection of amino groups in peptide synthesis. They are valuable synthetic intermediates for many heterocyclic compounds. Treatment of alcohols with **BTC** or **TCF** to generate the corresponding chloroformates, followed by further reaction with sodium azide afforded the azidoformates in high yields (75-96%) under mild conditions.

A near quantitative yield of chloroformates could be obtained by the slow addition of one equivalent of alcohols to a suspension of 0.75 equivalent of **TCF** and a catalytic amount of charcoal in dry THF. Without further purification, the chloroformates reacted with NaN_3 in dry acetone to get azidoformates **58** in high yields (75-96%) (*Scheme 25*).[34]



Scheme 26

TCF has been also employed for a one-pot preparation of azidoformates.[35] When various alcohols react with **BTC** in the presence of sodium azide and triethylamine under mild conditions, azidoformates are formed in excellent yields (*Scheme 26*). This method can also be



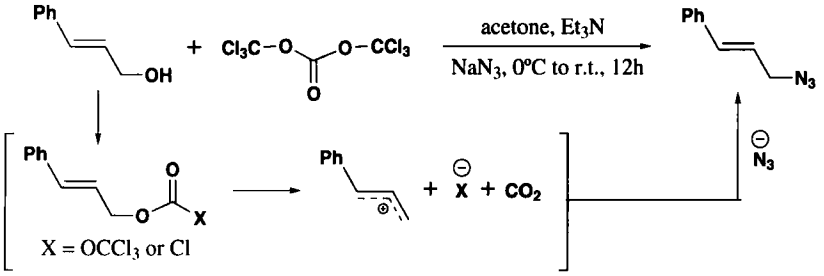
Scheme 26

employed for the synthesis of various chiral azidoformates from chiral alcohols. The diacetonide, readily available from D-glucose, was also efficiently transformed to the corresponding azidoformate in very good yield.

Azidoformates. General Procedure.-[35] *To a mixture of the alcohol (1.0 mmol) and sodium azide (2.0 mmol) in acetone (10 mL) was added triethylamine (1.5 mmol) at 0°C. The reaction mixture was stirred at this temperature for 15 min, then a solution of triphosgene (0.5 mmol) in acetone (5 mL) was added dropwise at 0°C over 15 min. The reaction mixture was stirred at this temperature for 1 h and slowly allowed to warm up to room temperature for 24 h. The reaction mixture was filtered to remove insoluble salts and the filtrate was diluted with water and extracted with EtOAc (3 x 20 mL), and the organic phase was washed with water (10 mL), brine (10 mL) and dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography to affoird the pure azidoformate in good yield.*

b. Preparation of Allyl Azides

Allyl azides are important synthetic intermediates and a source for synthetically useful allylamines. *Section 1.3a* discussed the reaction of **BTC** with aliphatic alcohols in the presence of sodium azide and triethylamine to afford azidoformates in excellent yields. Under similar reaction conditions, however, when **BTC** was added slowly to a mixture of cinnamyl alcohol, triethylamine and sodium azide in acetone at 0°C, cinnamyl azide was obtained as a major product (80%) while cinnamyl azidoformate was found to be only a minor product (20%).[36] Cinnamyl azide could nonetheless be obtained in excellent isolated yield (80%) and very high purity (>98%, GLC) by a minor modification of the experimental procedure. The formation of cinnamyl azide could be proceeding through the allyl carbonation, generated from trichloromethyl allyl carbonate or allyl chloroformate, with the concommitant evolution of carbon dioxide, followed by nucleophilic addition of azide ion (*Scheme 27*). This reaction represents a simple and efficient one-pot method for the preparation of allyl azides directly from allyl alcohols using **BTC** and sodium azide.



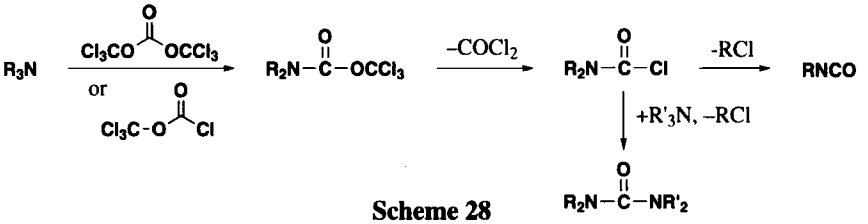
Scheme 27

Cinnamyl Azide. Typical Procedure.-[36] *To a stirred solution of triphosgene (1.48 g, 5.0 mmol) in acetone (20 mL) was added a solution of cinnamyl alcohol (1.34 g, 10.0 mmol) and Et_3N (1.51 g, 15.0 mmol) at 0°C. The reaction mixture was stirred for 20 min and then at r.t. for 3 h, then*

cooled back to 0°C and sodium azide (1.30 g, 20.0 mmol) was added in one portion. The mixture was stirred at this temperature for 1 h and kept at r.t. for 12 h. Then H_2O (20 mL) to the mixture was added and extracted with Et_2O (3 x 20 mL). The organic layer was washed with brine (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure at r.t. to give pure cinnamyl azide as yellow oil (1.28 g, 80%).

II. REACTIONS WITH AMINES

The reaction of **TCF** and **BTC**, acting substitutes phosgenating reagents with amines, has been used more extensively in organic reactions. Amines are highly reactive nucleophiles and thus are easily used for preparation of carbamoyl chlorides, isocyanates and ureas (*Scheme 28*). The advantages of this method are simple operation, mild reaction conditions and excellent yields.

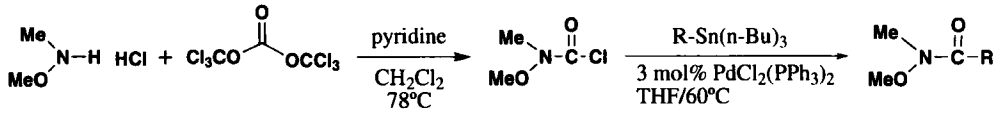


Scheme 28

1. Preparation of Carbamoyl Chlorides

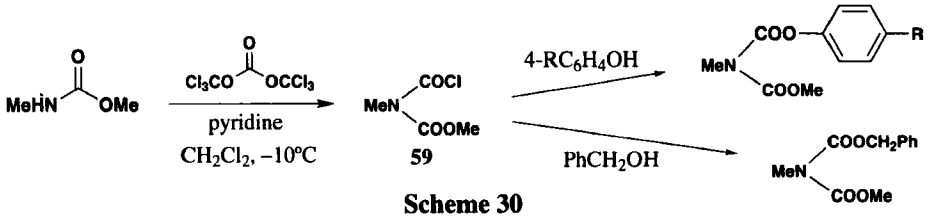
Carbamoyl chlorides can be used as versatile intermediates in the synthesis of ureas, carbamates or heterocyclic derivatives by treatment of corresponding amine with **TCF** or **BTC**. Generally, the product can be obtained from amines in DMF in the presence of base, such as pyridine, or triethylamine.

Murakami *et al.* reported a modified method for the preparation of *N*-methoxy-*N*-methyl carbamoyl chlorides using **BTC**; this intermediate is reported to be a useful synthetic block to construct *N*-methoxy-*N*-methylamides, catalyzed by palladium reagents in good yield (*Scheme 29*).[37]



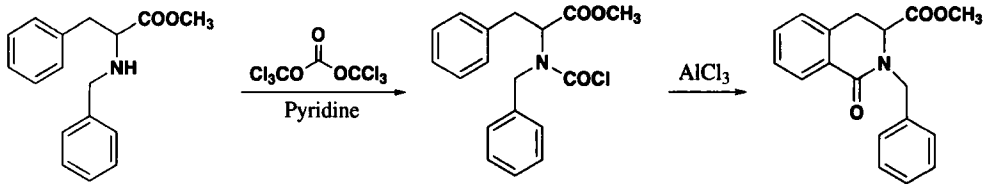
Scheme 29

Similarly, the intermediate **59** obtained from **BTC** and methyl *N*-methylcarbamate reacts with phenols and alcohols to give the corresponding carbamates (*Scheme 30*).[38]



Scheme 30

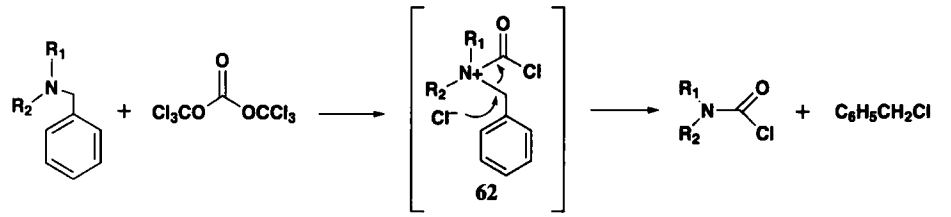
N-Benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester **61** was also synthesized successfully by treatment of *N*-benzylphenylalanine methyl ester **60** with **BTC**, followed by cyclization in the presence of $AlCl_3$ (*Scheme 31*).[39]



60 **61**

Scheme 31

Recently, **BTC** has been used for the direct conversion of benzylamines into carbamoyl chlorides (*Scheme 32*).[40] Tertiary amines react smoothly with **BTC** to give the expected products *via* the formation of an ammonium intermediate **62**.



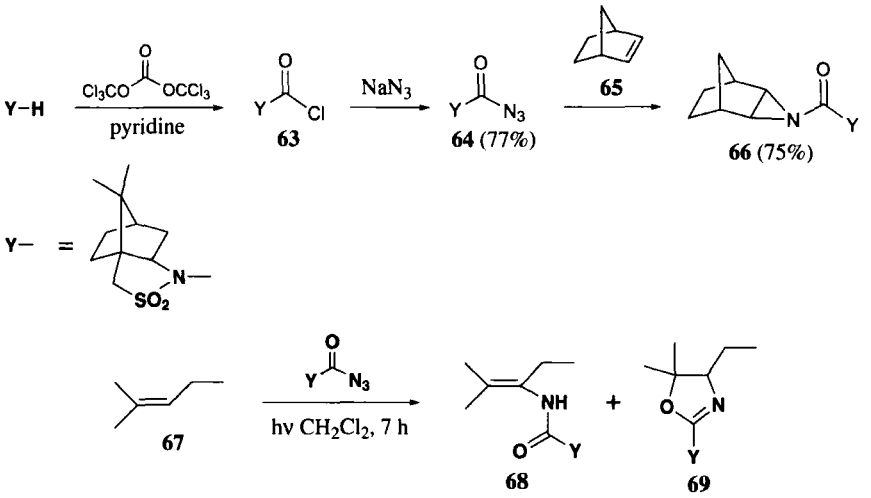
Scheme 32

5-Fluorouracil (5Fu) is of interest as a potential antitumor agent, having activity comparable to the clinically used compounds. Reaction of 5Fu with **TCF** has been used recently for the synthesis of chloroformyl 5Fu, which is linked to a spacer hydroxyl group of **PEG** that served as a macromolecular linking arm between SF and 5Fu. It may offer improved therapeutic effect.[41]

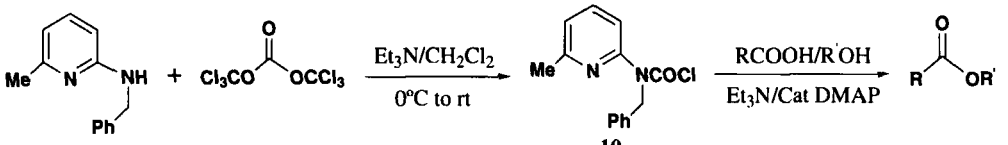
An interesting example of this reaction reported by Signore and co-workers is the synthesis of a carbamoyl azide, which can be used as a chiral aminating agent.[42] Compound **63**, generated from Oppolzer's sultam by reaction with **BTC** in toluene in the presence of pyridine, gave carbamoyl azide **64** in high yields upon addition of sodium azide. The latter compound readily reacted with norbornene **65** to afford the corresponding aziridine **66** (*Scheme 33*).

Similarly, prochiral alkene **67** reacts with **64** to form the substituted allyli amine **68** and the oxazoline **69**, with all the amination products showing good diastereoselectivity (*Scheme 34*).

Some carbamoyl chlorides can act as esterifying agents of many of primary or secondary aliphatic carboxylic acids or alcohols to yield the corresponding esters,[43] such as *N*-benzyl-2-(6-methyl)pyridinecarbamoyl chloride **70** (*Scheme 34*). The reagent **70** is stable and was prepared conveniently. This method provides a highly effective route to various carboxylic esters, although the esterification of aromatic carboxylic acids are more sluggish than those of aliphatic acids.



Scheme 33

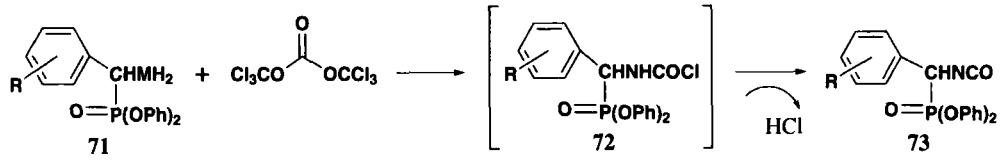


Scheme 34

2. Preparation of Isocyanates

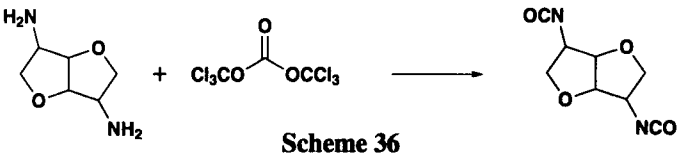
A widely used method for preparation of isocyanates is the treatment of primary amines or their salts with **TCF** or **BTC**, which is viewed to yield carbamoyl chlorides which then undergo spontaneous dehydrohalogenation. The most common procedure for the synthesis of isocyanates involves in the slow addition of the amine to a solution of TCF or BTC at low temperature, stirring at room temperature and subsequent reflux. The desired product can then be obtained by distillation.

α-Isocyanatoalkylphosphonic acid diphenyl esters **73** are the main products obtained from α-aminoalkylphosphonic acid diphenyl esters **71** and **BTC** possibly *via* intermediate **72** (*Scheme 35*).[44]



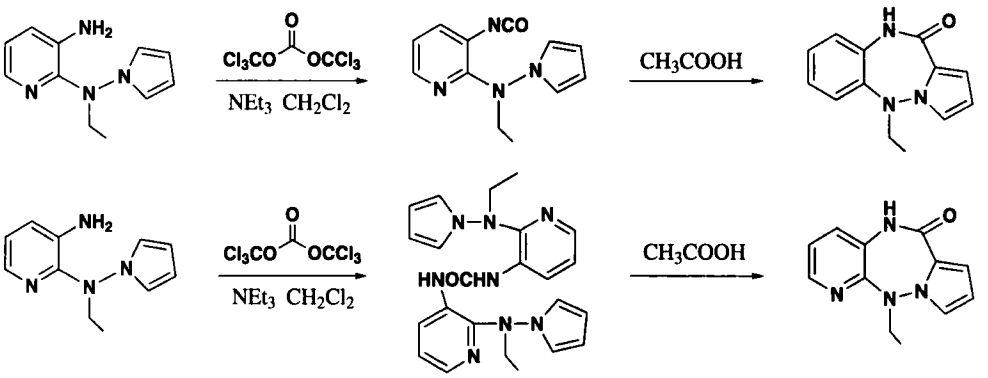
Scheme 35

Treatment of the diamino compound (*Scheme 36*) with **TCF** instead of phosgene, leads to the corresponding diisocyanate.[45] This type of diisocyanate monomer can be used to prepare polyurethane through a polymerization procedure.



Scheme 36

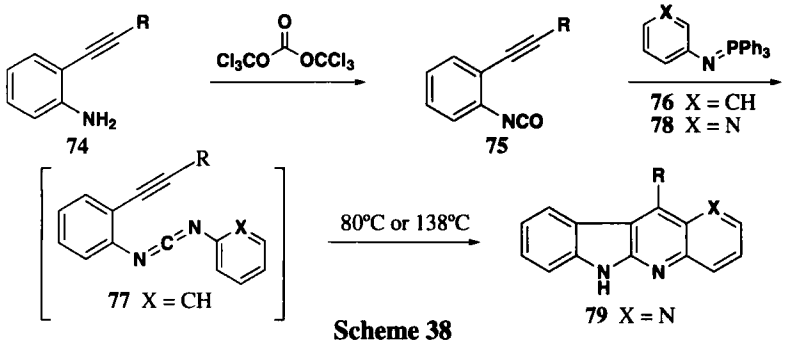
Recently, a series of isocyanates has been employed in broader fields such as supermolecular,[46] and biological chemistry.[47,48] As shown in *Scheme 37*, some isocyanates were



Scheme 37

cyclized to the lactams in acidic medium to give products which can be effective against the *HIV-1* multiplication in infected cells. Not all amines will generate isocyanates upon treatment with **TCF** or **BTC;** instead some give the substituted ureas which can also be cyclized in acidic medium.[49] These reactions we will discussed more in *Section II.3c*.

The reaction of **BTC** with **74** yielded the corresponding isocyanate **75**, which upon an *aza*-Wittig with the iminophosphorane **76** generated the benzoenynyl carbodiimides **77,** which then produce a variety of indolonaphthyridines by thermolysis (*Scheme 38*). The other



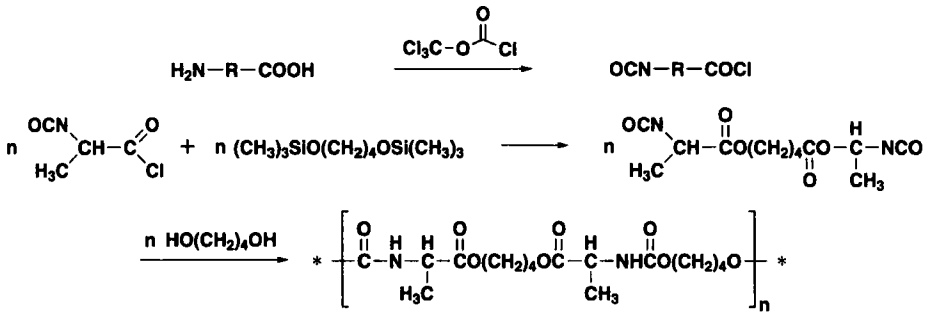
Scheme 38

iminophosphorane **78** can also be used for the *aza*-Wittig reaction with **75** instead of **76** to synthesize 6H-indolo[2,3-b][1,5] naphthyridines **79** as the major products, which can be considered as the 5-aza analogues of ellipticines merging the heterocyclic frameworks of both ellipticine and indoloquinoline. This is shown to be a convenient method to synthesize a variety of

indolonaphthyridines, whose structures resemble ellipticine alkaloids and are good candidates as DNA intercalating agents with potentially interesting biological activities.[50]

Iwakura *et al.* reported the synthesis of α-isocyanatoacyl chlorides by treatment of amino acid hydrochlorides and **TCF** in 1,4-dioxane. Although this route gave lower yields, this phosgene-free method provides a simple and conventional one-step procedure.

The reaction of α-isocyanatoacyl chloride with silylated alcohols can form the isocyanate esters. Similarly, poly(isocyanato esters) can be obtained in high purity and good yields from mono-α-amino acids and common polyols. Those new isocyanates have been tested for the synthesis of long-term stable and degradable polyurethanes. Significantly, this method provides a novel preparation of polyurethanes in the absence of catalysts (*Scheme 39*).[51]



Scheme 39

One of the most common methods for preparation of ureas is the reaction of isocyanates and amines. The isocyanates were used in the next step without purification. For example, the synthesis of *spin-labeled* RNA,[52] of 1-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)-3-{4-(1-hydroxy-1-methylethyl)-furan-2-sulfony]} urea,[53] and of tetrakis(*o*-nitrophenyloctylureamethyl)cavitand.[54] These reactions will be discussed in detail in *Section II.3c*.

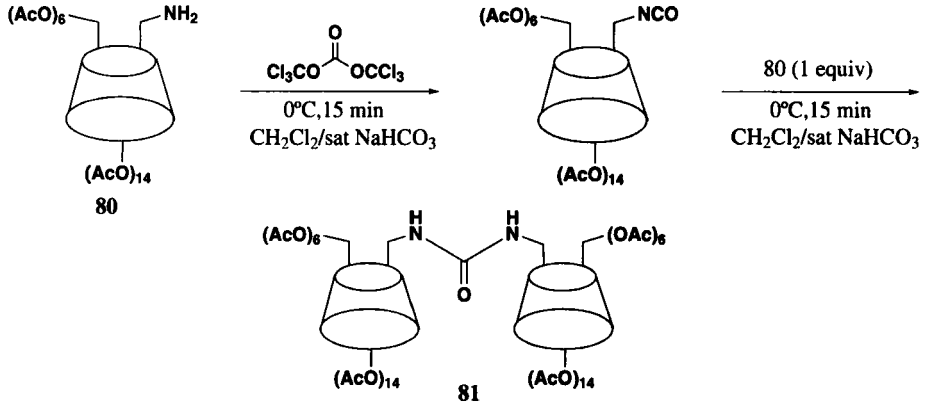
3. Preparation of Ureas

The synthesis of urea derivatives has recently become the focus of several investigations. Since the urea functionality is a key structural element which serves as a non-hydrolyzable surrogate of amide bonds in many pharmaceutically active molecules.[55,56] An effective and convenient synthesis of ureas is of great interest in drug discovery in the chemical, biochemical and dye industry.[57]As is well known, the most common method to obtain urea is by phosgenation of amines. When excess **TCF** or **BTC** reacts with amines under the proper conditions, carbamoyl chlorides or isocyanates are obtained directly in good yields, while with an excess of the amines, ureas are formed in excellent yields.

a. Synthesis of Symmetrical Ureas

Recently, dimeric derivatives have become common intermediates for the generation of pro-drugs. Urea acts as a bridge to link two identical structural molecular units during preparation of these dimers. When **TCF** or **BTC** is treated with an excess of primary or secondary

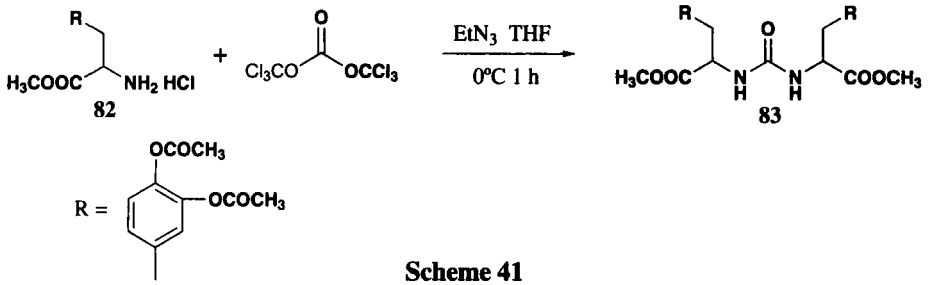
amine, symmetrical ureas are produced in high yields. An interesting example is the synthesis of cyclodextrin dimers.[58] Cyclodextrins have been widely used in many applications and cyclodextrin dimers can improve binding properties. Urea-linked β-cyclodextrin dimers **81** are produced by treatment of 6-amino-6-deoxy-β-D-cyclodextrin **80** with **BTC** in a mixture of CH_2Cl_2-saturated aqueous $NaHCO_3$, followed by addition of another equivalent of **80** (*Scheme 40*). This constitutes a novel one-pot, two-step route to obtain β-cyclodextrin dimers.



Scheme 40

Compound 81. Typical Procedure.-[58] *The amine **80** was divided into two equal portions. One portion was dissolved in an 1:1 CH_2Cl_2-saturated aqueous $NaHCO_3$ mixture (12 mL), cooled to 0°C in an ice bath and then treated with solid **BTC** in a single portion (6.5 mg, 0.022 mmol). After 15 min of vigorous stirring, the other portion of amine **80** was added and stirring was continued at room temperature for 15 min. Conventional work-up and column chromatography afforded cyclodextrin dimer **81** (127 mg, 49%).*

Dimeric L-dopa derivatives **83** were also prepared by the condensation of **BTC** with **82** in the presence of triethylamine (*Scheme 41*). The compound **83** showed good physicochemical properties and chemical stability in aqueous buffer solutions.[59]

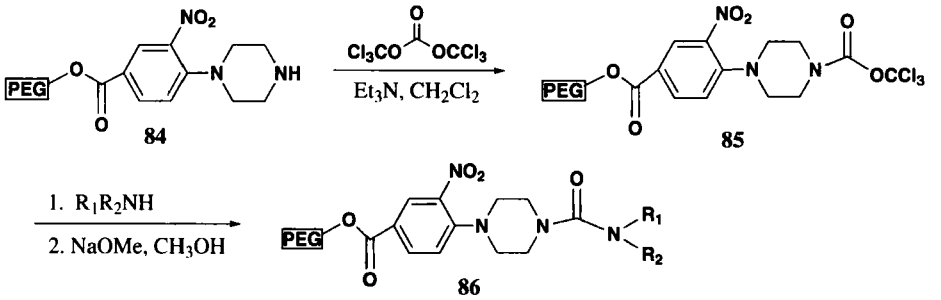


Scheme 41

b. Synthesis of Unsymmetrical Ureas

Combinatorial organic synthesis has been regarded as an important tool for the preparation of a large number of pharmaceutical compounds such as asymmetric ureas and has become most common method to combine functional groups in different fields.

Addition of PEG-bound diamine **84** to **BTC** in the presence of triethylamine leads to the trichloromethyl carbamate intermediates **85**, which readily reacts with primary or secondary amines to produce the substituted ureas **86** (*Scheme 42*).[60] Many types of ureas could be accessed by this route.



Scheme 42

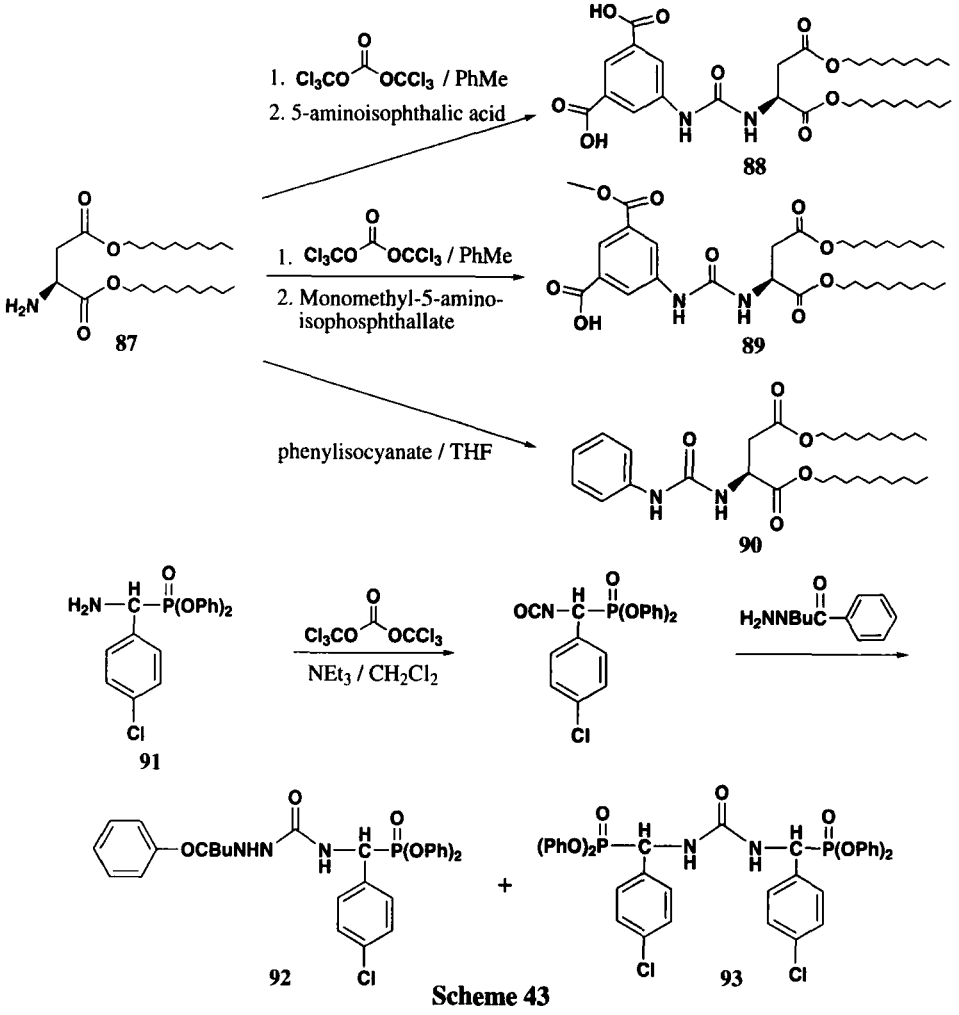
Similarly, treatment of the *bis-o*-decylaspartate **87** with **BTC** converts it to the isocyanate which, upon coupling with various amino acids, affords a series of gelators **88-90** (*Scheme 43*). It was demonstrated both the urea and the carboxylic acid groups play key roles during self-association and gelation.[61]

However, during the reaction of α-aminoalkylphosphonates **91** with **BTC** to obtain target compound **92,** a small amount of by-product **93** was detected. The desired product **92** may be obtained in higher yield by control of the rate of addition of **91** at lower temperature (*Scheme 43*).[62]

Compound 92. Typical Procedure.-[62] *A solution of α-aminoalkylphosphonate **91** (1 g, 2.68 mmol) and triethylamine (8.04 mmol) in methylene chloride (10 mL) was added dropwise to a solution of **BTC** (0.40 g, 1.34 mmol) in methylene dichloride (10 mL) during 2 h under at –15°C, and the resulting mixture was stirred at room temperature for 1 h. A solution of N-tert-butyl-N-substituted benzoylhydrazine (2.41 mmol) in methylene dichloride (10 mL) was added and the mixture was stirred at room temperature for 8 h. After the solvent was removed under vacuum, the residue was dissolved in ethyl acetate (20 mL) and filtered. The filtrate was evaporated and the residue was purified by vacuum column chromatography on silica gel using petroleum ether (60-90°C) and ethyl acetate as the eluent to afford **92** as a colorless crystalline solid 1.02 g (83%).*

The reaction of the corresponding amines and isocyanates easily afford the diarylureas which are useful as a valuable agents to prepare porphyrin dimers and trimers.[63] Treatment of aminoporphyrin **94** with **BTC** in dry dichloroethane containing a small amount of dry pyridine,

followed by another mole of **94** led to porphyrin dimer **95** in 73% yield. In a similar way, the monomer **96** was also prepared from **94** and aniline in 90% yield (*Scheme 44*). There is a considerable body of research on the synthesis of porphyrin derivatives by this method.[64,65]

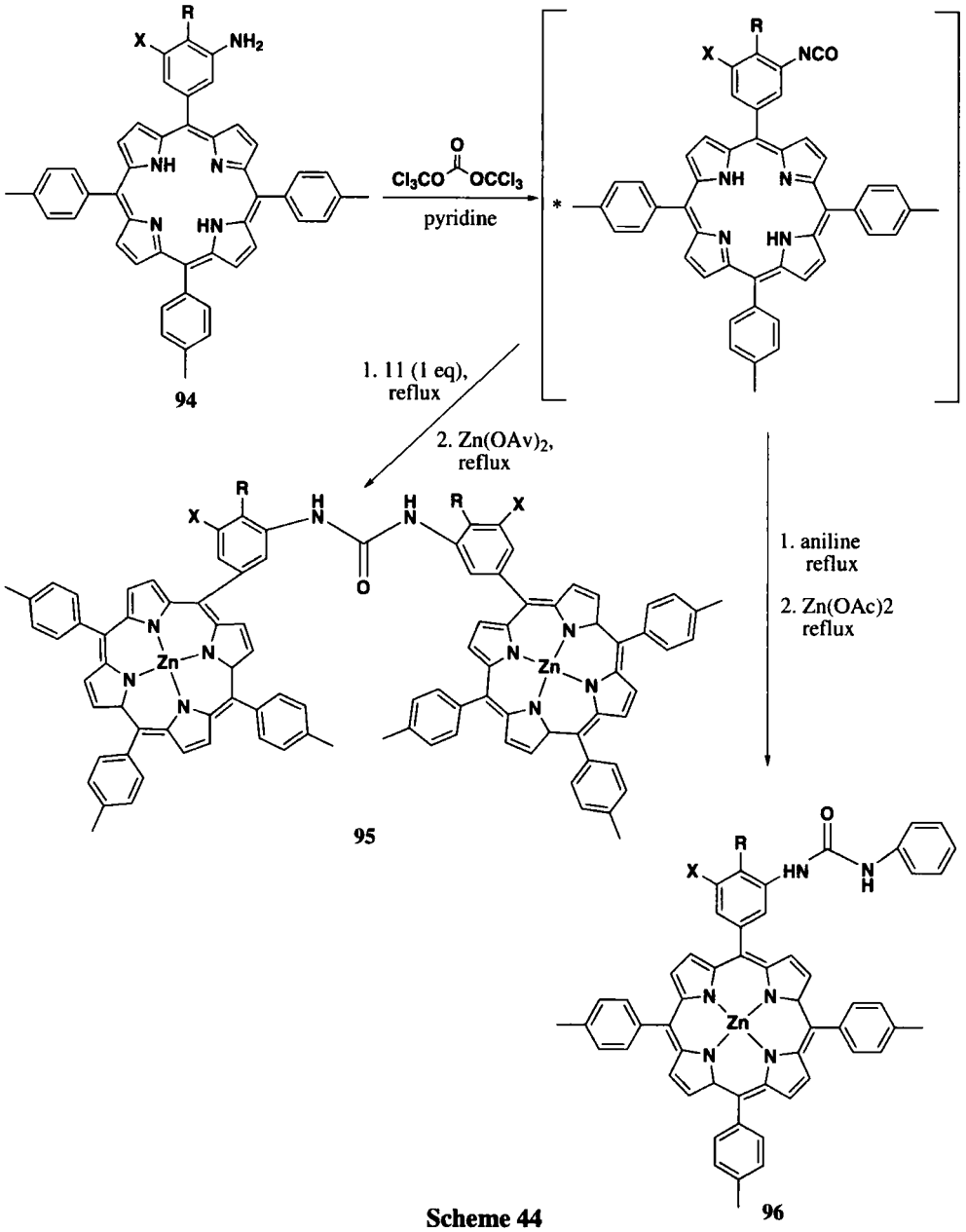


Scheme 43

When one equivalent of 4.0-*tetrakis*(*o*-aminophenyl)porphine (4.0-TAPP) was treated with two equivalents of the diamine in CH_2Cl_2, no polymeric or oligomeric by-product was detected; a high selectivity for intramolecular isocyanato-amine coupling was observed.[66]

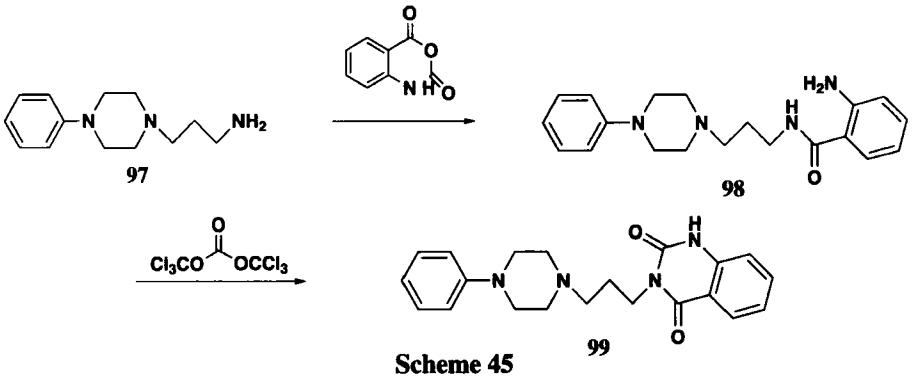
c. Synthesis of Cyclic Ureas

Compounds containing either two primary or secondary amino groups, can form cyclic ureas within the same moleculeupon treatment with **BTC**, such as in the synthesis of tricyclic pyridopyrrolopyrimidone[67] and some fluorinated uracil derivatives,[68] which may have potential biological activity.



Scheme 44

Garcia[69] developed a simple and efficient method to prepare pelanserine, which is considered to be a well-documented potential antihypertensive agent. Thus amine **97** reacts with isatoic anhydride to a product which subsequenty cyclizes with **BTC** to give the pelanserine **99** (*Scheme 45*).

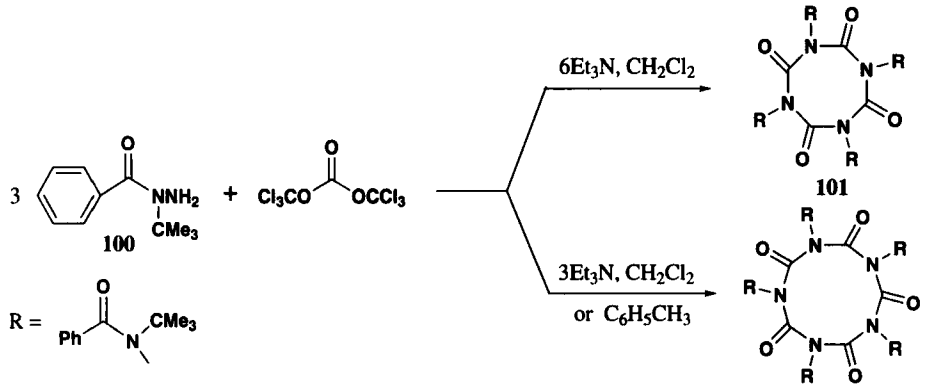


Scheme 45

Pelanserine 99. Typical Procedure.-[69] *A solution of* ***98*** *(1.2 g, 5.0 mmol) in methylene chloride (50 mL) was added a solution of BTC (0.5 g, 1.7 mmol) in methylene chloride (10 mL) at room temperature. The mixture was then refluxed for 2 h. The organic phase was washed with water and dried over* $MgSO_4$. *Removal of solvents under reduced pressure gave a solid which was then recrystallized from ethanol to give 1.55 g (88%) of* ***99****.*

When L-cystine dimethyl ester reacted with **BTC** under high dilution conditions, a mixture of two symmetrical cyclic oligoureas was obtained.[70] These urea groups bearing multiple units of hydrogen bonding sites which are symmetrically distributed and converge toward the center of the cavity, make them suitable for molecular recognition of anionic substrates with spherical shapes.

Interestingly, the reaction of amines with **BTC** in the presence of different ratios of base can lead to different products. Three equivalents *N-tert*-butyl-*N*-benzoylhydrazine **100** reacted with **BTC** using six equivalents of triethylamine to yield cyclic tetramer **101** in 65% yield. In the absence of base or when only three equivalents of base was used, cyclic pentamer **102** was generated in 95% and 91% yields, respectively (*Scheme 46*).[71]

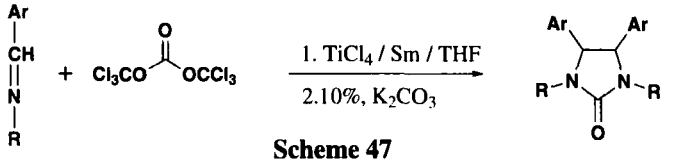


Scheme 46

1,3,5,7-tetra-N(-tert-Butylbenzamido)-[1,3,5,7]tetrazocane-2,4,6,8-tetrone (101). Typical Procedure.-[71] *A solution of* ***BTC*** *(0.26 g, 0.87 mmol) in methylene chloride (10 mL) was added*

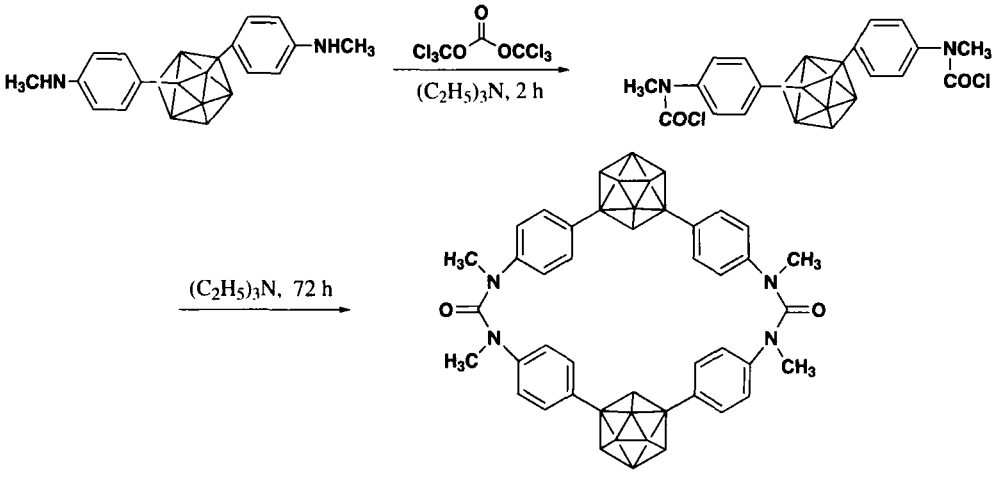
dropwise to a solution of N-tert-butyl-N-benzoylhydrazine ***100*** *(0.5 g, 2.6 mmol) and distilled triethylamine (0.53 g, 5.22 mmol) in methylene chloride (10 mL) at –15°C. After the addition, the mixture was stirred for 3 h at –15°C and 2 h at room temperature. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate (20 mL). The solid was filtered off and the filtrate was evaporated. The residue was purified by column chromatography on a silica gel using a mixture of petroleum ether (60-90°C) and ethyl acetate as the eluent. Finally, an analytical sample* ***101*** *was obtained in 65% yield, mp 160-162°C.*

Substituted imidazolidine-2-ones were synthesized in good yields by reaction of imines and **BTC,** promoted by a low-valent titanium reagent generated from a Ti/Sm system (*Scheme 47*).[72]



Scheme 47

A new family of macrocyclic compounds is composed of 1,7-dicarba-closo-dodecaborane moieties linked *via* their carbon vertices through *N,N'*-dimethyldiphenylurea groups. The synthesis of compound **103**, which shows a unique packing structure, is illustrated as an example in *Scheme 48*.[73]



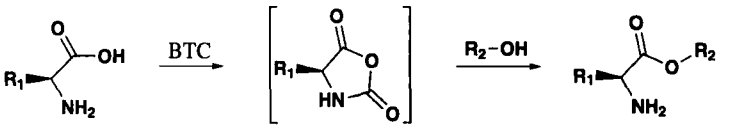
Scheme 48 **103**

III. REACTION WITH α-AMINO ACIDS AND α-AMINO ALCOHOLS

1. Reactions with α-Amino Acids to *N*-Carboxy Anhydrides (NCA)

α-Amino acids react readily with **TFC** or **BTC** to afford the five-membered ring compounds, *N*-carboxy anhydrides (NCAs) or Leuchs' anhydrides, whose preparation is exhaustively reported in the literature.[74] NCA has an active carboxylic acid group, which reacts easily with any nucleophilic entity to form esters, peptides and poly(amino acids).[75]

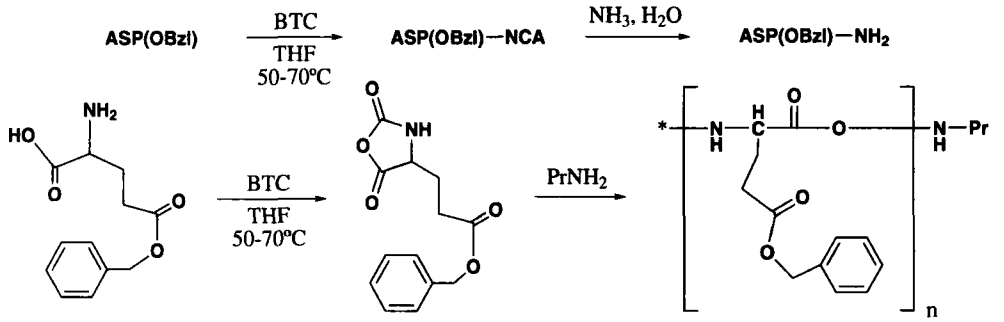
Alkyl esters of amino acids were prepared *via* the intermediate of NCA derived from **BTC** and **TCF**. When L-phenylalanine hydrochloride is treated with alcohols using **BTC**, L-phenylalanine esters were obtained without racemization in high yield (76-95%)[76] (*Scheme 49*).



Scheme 49

L-Phenylalanine Methyl Ester. Typical Procedure.-[76] *To a stirred solution of* L-*phenylalanine hydrochloride (15.02 g, 18.0 mmol) and TEA (10.86 g, 18.0 mmol) in anhydrous THF (50 mL) was added slowly a solution of* **BTC** *(20.01 g, 123.0 mmol) in* **THF** *(50 mL), After complete addition, the mixture was warmed to 55-60°C to allow complete dissolution, then methanol (10 mL) was added and the mixture was stirred for an additional half-hour. Excess solvent was evaporated in vacuo to give a white residue, which was neutralized (pH 7) with a NaOH (0.5%) solution. The mixture was extracted with ethyl acetate (2 x 50 mL) and the organic layer was dried (sodium sulfate). Removal of solvent under reduced pressure gave 12.67 g, (95%) of a white solid, mp 158-162°C,* $[\alpha]_D^{20} = -25.8$ *(c = 1 in EtOH).*

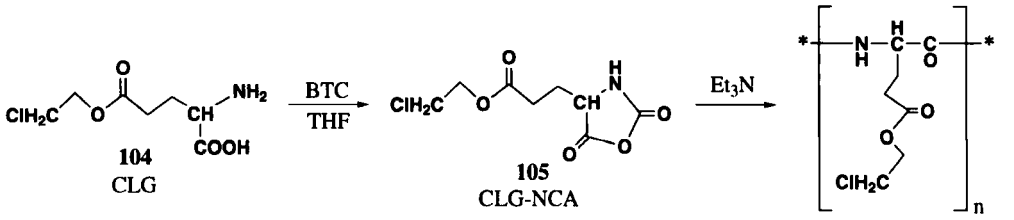
When NCAs react with amines, homopolypeptides or polypeptides were obtained. NCAs are valuable protected and activated amino acids, which are used for the preparation of peptides, but they are sensitive to moisture and prone to polymerization. (*Scheme 50*)[77,78]



Scheme 50

When **BTC** reacts with γ-chloroethyl glutamate **104**, a new poly(amino acid), γ-chloroethyl glutamate NCA **105** was obtained and could readily be transformed into polypeptide using triethylamine as the initiator (*Scheme 51*).[79, 80]

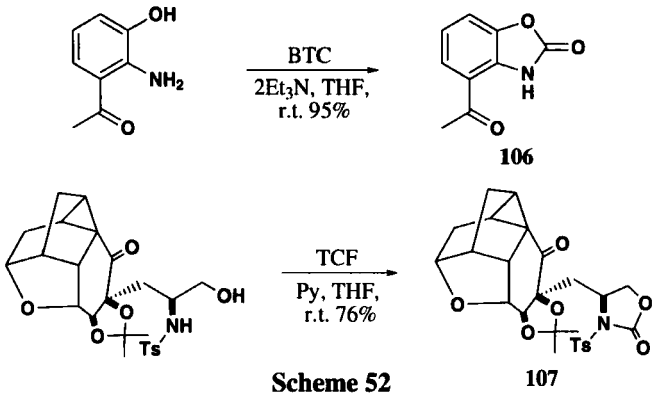
It was also reported that **BTC** acts as an efficient and inexpensive activating reagent for the solid-phase coupling of sterically hindered *N*-alkyl amino acid on highly acid labile trityl resin. When the novel **BTC** method in combination with HOAt/DIC coupling reaction was used, the linear cyclosporin O-undecapeptide was formed in high yield and purity.[81]



Scheme 51

2. Oxazolidinones by Reaction with α-Amino Alcohols

TCF and **BTC** have been utilized in the synthesis of oxazolidinone derivatives, serving as chiral auxiliaries.[82] Thus both of these reagents have proven very useful in the preparation of intermediates of natural products.[83-90] For example, 2-amino-3-hydroxyacetophenone was carbonylated to 4-ABOA (**106**) by means of **BTC** in the presence of a tertiary amine in 95%,[83] and compound **107** can be obtained with **TCF**.[85]

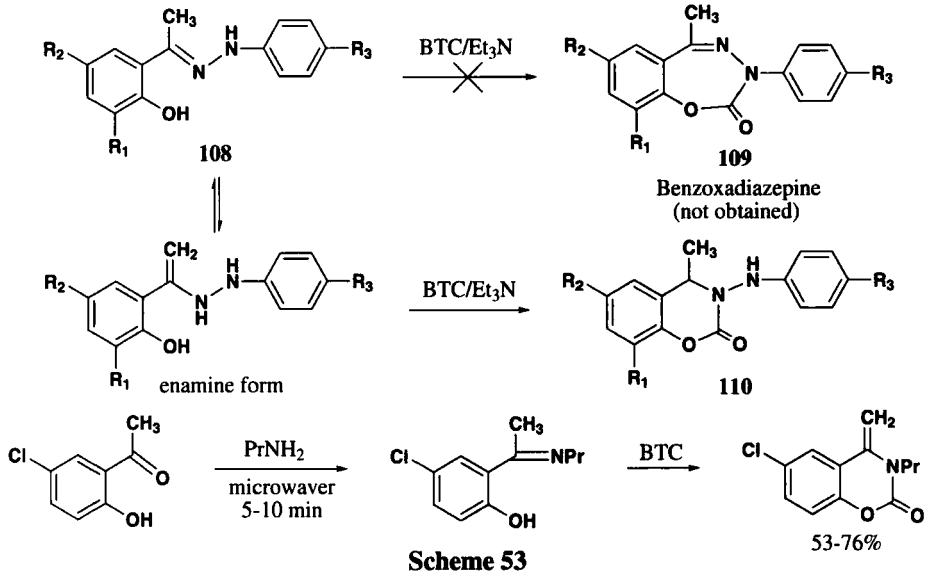


Scheme 52

Interestingly, the methyl group of **108** is involved in the cyclization step *via* the formation of the enamino form of **108**, which reacts with **BTC** to give the six-membered ring product **110** rather than the seven membered-ring benzoxadiazepine **109** (*Scheme 53*).[91,92]

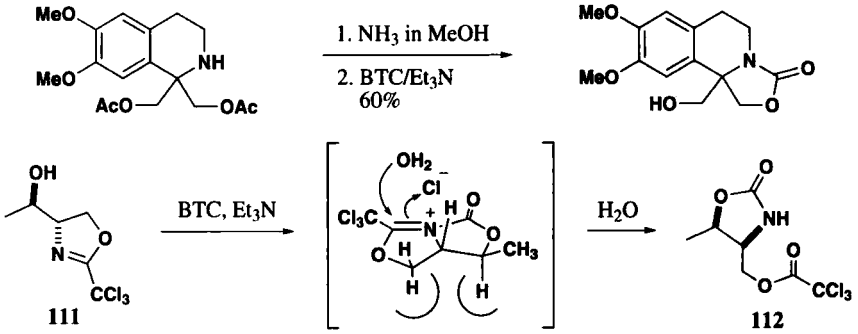
6-Bromo-4-methylene-3-(N-phenylamino)-3,4-dihydro-2H-1,3-benzoxazine-2-one. Typical Procedure.-[93] *To a stirred solution of the appropriate hydrazone (0.99 g, 3.0 mmol) and triethylamine (1 mL) in dichloromethane (30 mL) under nitrogen atmosphere was added a solution of* ***BTC*** *(0.45 g, 1.5 mmol) in dichloromethane (10 mL) dropwise over a period of 20 min. The mixture was stirred at room temperature for 1 h, then refluxed for 2 h and quenched with water. The organic layer was separated followed by extraction of the aqueous layer with dichloromethane (2 x 30 mL). The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting solid (0.64 g, 65%) was crystallized from ethyl ether.*

α-Amino acids and α-amino alcohols reacted with **TCF** and **BTC** to afford cyclic anhydrides and carbamates because they have two nucleophilic centers. *sec*- and *tert*-Amines



Scheme 53

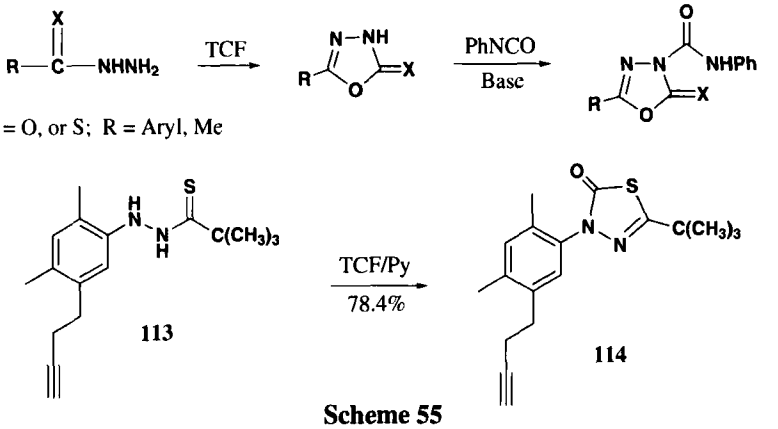
adjacent to esters or hydroxyl groups can also react with **TCF** and **BTC** to afford cyclic compounds.[95] Treatment of the mixture of isomers **111** with **BTC** and triethylamine,[96] generated the intermediate imidazonium ion in *situ* which was gradually hydrolyzed to produce oxazolidinone **112**.[94]



Scheme 54

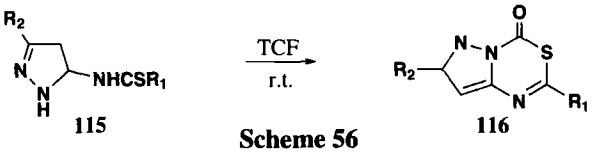
(4S,5R)-5-Methyl-4-(trichloroacetoxymethyl)oxazolidin-2-one (112). Typical Procedure.-[94] *To an ice-cooled solution of a mixture of* **111** *(75 g, 323.0 mmol) and triethylamine (58.5 mL, 419.0 mmol) in dry CH_2Cl_2 (1520 mL) was added* **BTC** *(38.3 g, 129.0 mmol) in portions, and the mixture was stirred at r.t. for 3 h. The reaction mixture was poured into saturated aq. NH_4Cl (1600 mL) at 0°C and stirred for 10 h. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography hexane/ethyl acetate (3:1 to 50:1) to afford* **112** *(70.1 g, 79%).*

5-Aryl-1,3,4-oxadiazol-2(3H)-ones can be conveniently prepared by reaction of **TCF** with arylhydrazines in inert solvents at temperatures ranging from room temperature to reflux in the presence of DMF or a tert-amine as catalysts. Oxadiazolones are often useful herbicides.[97] The reaction of **TCF** with **113**, 1,3,4-oxadiazol-2(3H)-one occurs smoothly in the presence of an acid acceptor to afford the new thiadiazolone herbicide IR 5790 (**114**)[98] directly in high yields; it exhibits both pre- and postemergence activity (*Scheme 55*).



Scheme 55

Treatment of **115** with **TCF** at room temperature gave the 2-substituted pyrazolo[1,5-c][1.3.5]thiadiazine-4-ones (**116**), which are new fungicides against the causal agent of rice blast disease, *magnaporthe grisea* (*Scheme 56*).[99]



Scheme 56

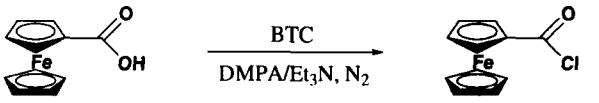
5-tert-Butyl-3-[2,4-dichloro-5-(2-propynyloxy)phenyl]-1,3,4-thiadiazol-2(3H)-one(11). Typical Procedure.-[100] *Pyridine (0.2 mL) and* **BTC** *(0.5 g, 2.5 mmol) were added to a solution of N-[2,4-dichloro-5-(2-propynyloxy)phenyl]-N-thiopivaloylhydrazine (**10**, 1.65 g, 5.0 mmol) in dioxane (25 mL), under a nitrogen atmosphere. After being stirred at room temperature for 3 h, the mixture was poured into water (250 mL) and extracted with diethyl ether (2 x 100 mL). The ethereal extracts were washed to neutrality with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by silica gel column chromatography with n-hexane/ethyl acetate (9:1) as the eluent to give 1.4 g (78%) of yellowish white power, mp 102-104°C.*

IV. CHLORINATION REACTIONS

1. Conversion of Carboxylic Acids to Acid Chlorides

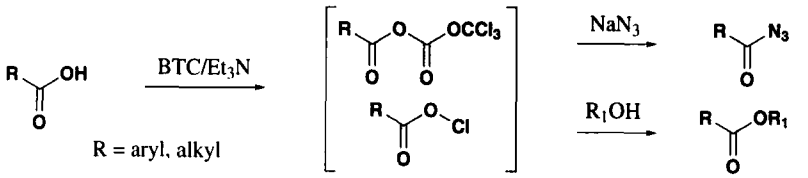
TCF and **BTC** are convenient reagents for the preparation of acid chlorides and anhydrides from carboxylic acids.[1] One of the claimed advantages of using **TCF** and **BTC** instead of phosgene is that lower molar ratios; even stoichiometric amounts may be used.

Ferrocenoyl chloride was conveniently prepared in high yield when **BTC** was treated with ferrocenecarboxylic acid in dichloromethane in the presence of triethylamine and DMAP (*Scheme 57*). This method is milder and cleaner without the formation of dark-colored impurities.[101]



Scheme 57

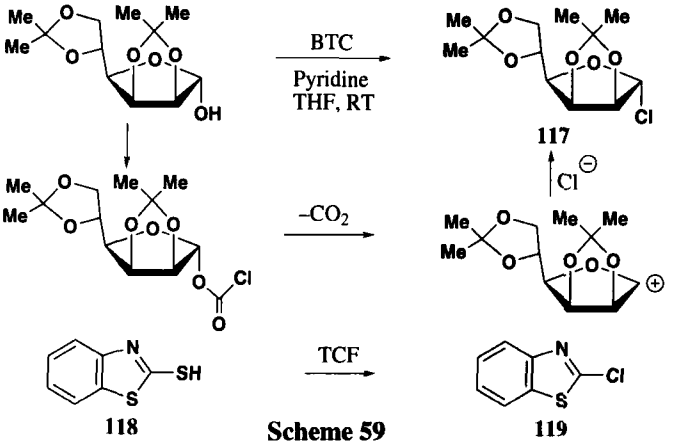
BTC has also been described as an acid activator in organic synthesis. A series of acyl and alkyl azides were prepared from carboxylic acids and sodium azide using **BTC** under very mild conditions, without rearrangement to isocyanates in the case of acyl azides. Bao *et. al,* also reported that aroyl azides can be obtained in high yields from the carboxylic acids and sodium azide in solution using **BTC**[102] (*Scheme 58*). As has already been discussed, **BTC** is a convenient esterification agent.[103]



Scheme 58

2. Chlorination of Alcohols and Thiols

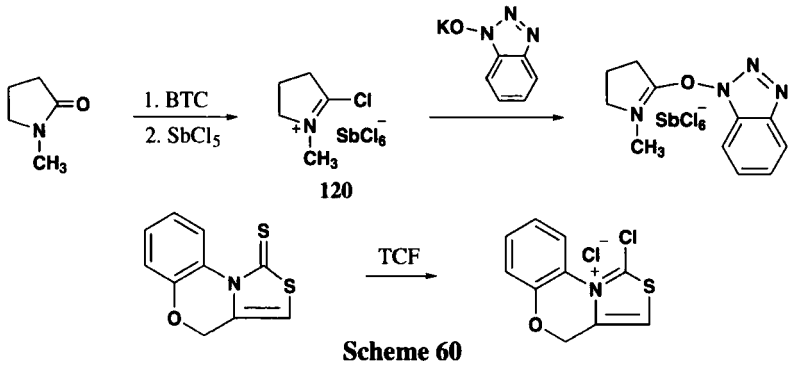
When an alcohol and a thiol reacted with **BTC** and **TCF**, alkyl chloride **117** was obtained as the final product through the intermediate formation of chloroformates. The advantage of this method is its compatibility with a variety of acid-sensitive protecting groups. Glycosyl chlorides were prepared by using **BTC** from available sugar hemiacetals in the presence of pyridine.[104] Treatment of **TCF** with 2-mercaptobenzothiazole **118** can produce 2-chlorobenzothiazole **119**, which is an important organic intermediate for the pesticides and drug industries (*Scheme 59*).[105]



Scheme 59

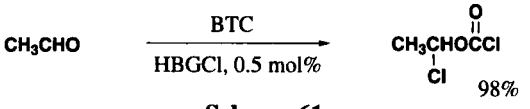
3. Chlorination of Ketones and Aldehydes

Compared with reagents such as thionyl chloride or phosphorus trichloride, **TCF** and **BTC** can be used as safe and clean reagents for the chlorination of ketones and aldehydes. *Scheme 60* illustrates that the condensation of *N*-methylpyrrolidone with **BTC** yielded the immonium chloride, which was subsequently converted to the intermediate 5-chloro-3,4-dihydro-1-methyl 2H-pyrrolium hexachloroantimonate **120** with $SbCl_5$, which is a key compound to the synthesis of 5-(1H-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2H-pyrrolium hexachloroantimonate (BDMP) (*Scheme 60*).[106]



Scheme 60

Flosser *et al.* have reported that 1-chloroethyl chloroformate can be obtained in quantitative yield by the reaction of acetaldehyde with **BTC** (*Scheme 61*) in the presence of catalytic amounts of hexabutylguanidinium chloride (HBGCl), which are excellent "naked halide" catalysts.[107]

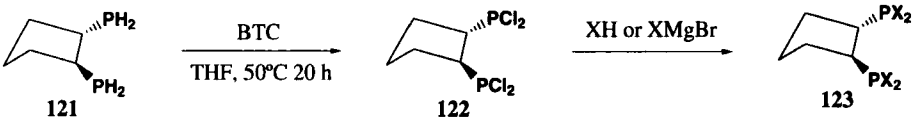


Scheme 61

4. Chlorination of RPH_2, PhP_3 and PhP_3O

The primary and secondary phosphanes RPH_2 were reported to produce *bis*(phosphorous dichlorides) $RPCl_2$ on treatment with reagents such as phosgene, **TCF** and **BTC** in inert solvents. Employment of **BTC** instead of phosgene led to the successful conversion of (1S,2S)-$C_5H_8(PH_2)_2$ (**121**) to the more versatile (1S,2S)-$C_5H_8(PCl_2)_2$ (**122**)[108] in quantitative yield (*Scheme 62*). Compounds **122** and **123** are important chiral bidentate phosphorus ligands in organic synthesis, which can couple with oxygen, nitrogen, and carbon nucleophiles.[109]

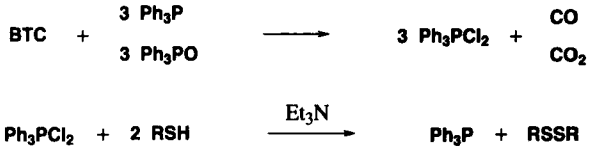
(1S, 2S)-$C_5H_8(PCl_2)_2$. General Procedure.-[108] *A solution of* **BTC** *(23.7 g, 80.0 mmol) in THF (250 mL) was added dropwise over 2 h to a stirred solution of 8.1 g (60.0 mmol) of (1S,2S)-$C_5H_8(PH_2)_2$ (**121**) in THF (400 mL) and the mixture was heated with stirring to 50°C. Evaporation of the solvent followed by distillation of the residue in vacuo (oil pump, bath temperaure 80-110°C) yielded 10.8 g (66%) of* **122** *as a colorless liquid.*



PX = P(OMe)$_2$(**1**), P(OPh)$_2$(**2**), P[2-OC$_{10}$H$_6$C10H$_6$O-2-(R)(**3**), P[OCH(Me)Et-(S)]$_2$(**4**), P(NC$_4$H$_8$O-cyclo)$_2$(**5**), P(C$_6$H$_{11}$O-cyclo)$_2$(**6**)

Scheme 62

Cotarca *et al.* reported that Ph_3P/**BTC** is a better chlorinating agent, which allows the complete chlorination of alcohols.[1] Su *et al.* used the system of Ph_3P/BTC/Et_3N and Ph_3PO/BTC/Et_3N to prepare disulfides from thiols by a one-pot procedure (*Scheme 63*). A possible mechanism for this activation has been proposed.[110]

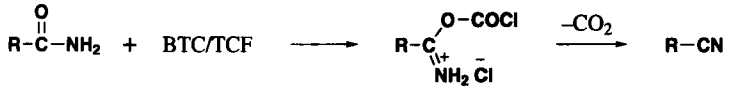


Scheme 63

V. AS DEHYDRATING AGENTS

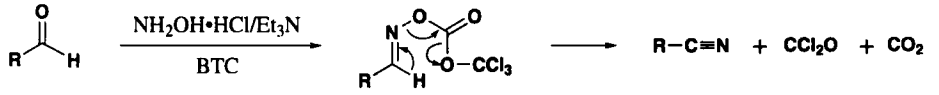
1. Preparation of Nitriles

Like phosgene, **TCF** and **BTC** have proven to be useful dehydration agents.[111] Nitriles can be obtained from carboxamides by using **TCF** and **BTC**.



Scheme 64

Nitriles could be also prepared from corresponding aldehydes and NH_2OH•HCl in high yields using **BTC**. The reaction is usually carried out in the presence of an acid acceptor, such as a tertiary amine.[112] Aliphatic and aromatic aldehydes were converted to the corresponding nitriles in good yields.



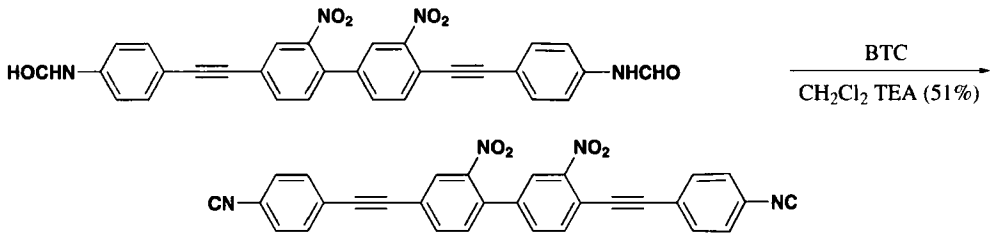
Scheme 65

4-Hydroxy-3-methoxybenzonitrile. Typical Procedure.-[112] *Hydroxylamine hydrochloride (0.38 g, 5.5 mmol) was added slowly to a stirred ice-cooled solution of 4-hydroxy-3-methoxybenzaldehyde (0.87 g, 5.0 mmol) in dry $CHCl_3$ (15 mL) and Et_3N (1.54 mL, 11.0 mmol) at such a rate that*

the temperature remained below 5°C. The reaction mixture was allowed to warm to room temperature and stirred for another 3-4 h. After the oxime had been formed, ***BTC*** *(1.65 g, 5.4 mmol) was added in portions over a period of 15 min. After each addition, an exothermic reaction was observed. The resulting mixture was stirred at room temperature for an additional 2 h; the progress of the nitrile formation was monitored by TLC. On completion of the reaction, it was quenched with H_2O (5 mL) and extracted with $CHCl_3$ (2 x 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and the solvent was removed in vacuo to afford the crude product which was purified by column chromatography (EtOAc/hexane, 1:9 v/v) on silica gel to afford pure 0.71 g, (95%) of 4-hydroxy-3-methoxybenzonitrile.*

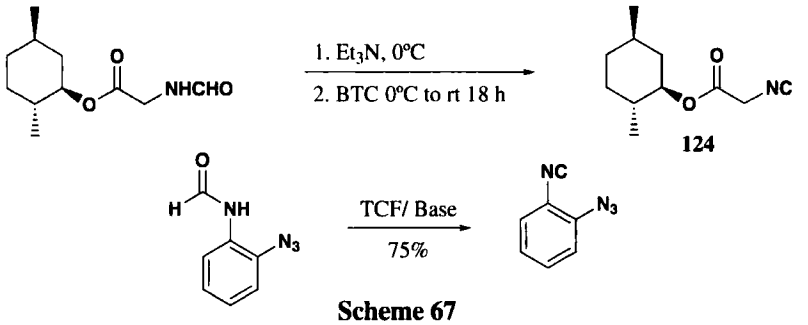
2. Preparation of Isocyanides

Isocyanides are the only class of stable organic compounds with a formal divalent carbon. Even though dozens of methods for the preparation of isocyanides have been described,[113] the best method for the preparation of isocyanides is the dehydration of formamides with phosgene or its surrogates such as **TCF** and **BTC** as dehydration reagent under mild conditions.[1,114] A



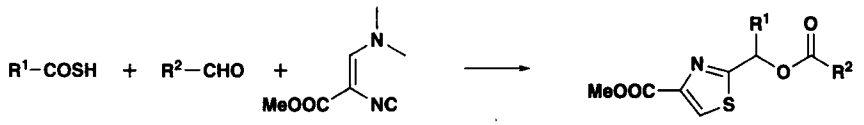
Scheme 66

large number of aryl and alkyl isocyanides, including chiral isocyanides **124**,[116-118] have been prepared by using stoichiometric amounts of formamides and **BTC** in solvents such as dichloromethane, chlorobenzene or *o*-dichlorobenzene.[115]



Scheme 67

Isocyanides, especially TosMIC, have demonstrated utility as intermediates for the preparation of a wide variety of compounds such as heterocycles, alkaloids, amino acids and peptides, steroids, ketones, metal complexes, antibiotics etc.[119] Isocyanides can participate in multi-component reactions (MCR) as illustrated in *Scheme 68* for example.[120]



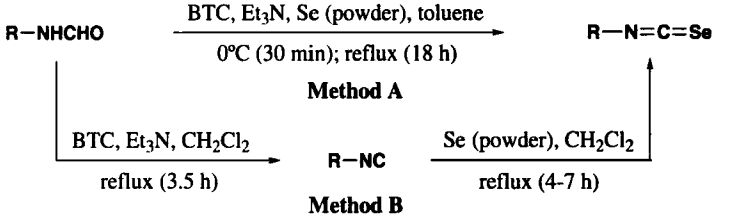
Scheme 68

(1R,2R,5R)-2,5-Dimethylcyclohexyl-2-formamidoacetate. Typical Procedure.-[121] *To a small flask that was charged with the formamide (5.0 mmol), was added 5 mL of CH_2Cl_2 followed by triethylamine (20.0 mmol). The reaction mixture was cooled to 0°C followed by the dropwise addition of* ***BTC*** *(590.0 mmol). The reaction mixture was allowed to warm to room temperature with continuous stirring for 18 h. After the reaction mixture was filtered to remove triethylamine hydrochloride, the solvent was removed under reduced pressure and then the crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane to afford 818 mg (73% yield) of the target isocyanide.*

3. Preparation of Isoselenocyanates and Isothiocyanates

Organoselenium compounds are of particular interest as intermediates in organic synthesis due to their many applications and biological activities.[122] Selenoureas, especially useful reagents for the synthesis of selenium-containing heterocycles, has been prepared from isoselenocyanates directly.

A modification of Barton's procedure[123] has been reported using **BTC** as a good substitute for phosgene.[124] As it is well known, most of isocyanides are volatile and have a repulsive odor. *Scheme 69* illustrates the fact that the intermediate isocyanides obtained from formamide and **BTC** need not be isolated and may be used for further reaction without purification.

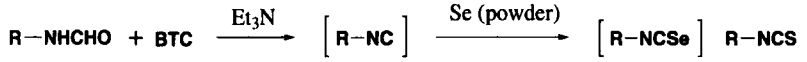


Scheme 69

In method B (*Scheme 69*), diisoselenocyanates could be obtained in high yields, without occurrence of the side-reaction, namely polymerization of diisocyanides, which occurs at high temperatures and upon prolonged reaction times.[125]

1,4-Diisoselenocyanatobenzene (Method B). Typical Procedure.-[125] *To a refluxing mixture of the 1,4-diformamidobenzene (0.25 g, 1.5 mmol), triethylamine (6.4 mol) in CH_2Cl_2 (5 mL) and 4 Å molecular sieves was added dropwise a solution of* ***BTC*** *(0.24 g, 0.8 mmol) in CH_2Cl_2 (2 mL) over a period of 1 h. After the addition, the mixture was refluxed for 2.5 h and then, selenium powder (0.24 g, 3.0 mmol) was added and reflux was continued for an additional 4-7 h; conventional work-up and column chromatography afforded 0.34 g (80%) of 1,4-diisoselenocyanatobenzene.*

Isothiocyanates are also important intermediates for the preparation of both sulfur and nitrogen containing organic compounds and especially heterocycles.[126] Isothiocyanates were prepared from formamides and sulfur powder with **BTC** (*Scheme 70*).[127]



Scheme 70

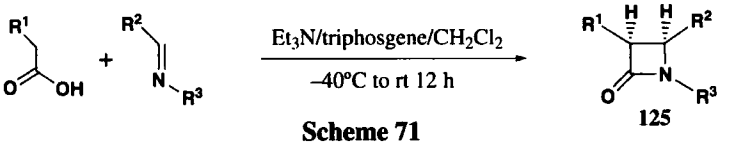
In this reaction also, the intermediate isocyanide can be used for the further reaction without isolation because it reacts with sulfur to give the isothiocyanate in the presence of catalytic amount of selenium powder. Furthermore, the rate of formation of isocyanide is relatively slow compared to the formation of isothiocyanate.

4-Chlorophenylisothiocyanate. Typical Procedure.-[127] *A solution of* **BTC** *(1.1 mmol) in dry CH_2Cl_2 (20 mL), was added dropwise over 1 h to a boiling suspension of p-chlorophenylformamide (3.0 mmol), selenium powder (0.5% mol of the formamide), sulfur powder (3.0 mmol), triethylamine (6.6 mmol), and CH_2Cl_2 (40 mL). After it had been stirred at reflux for the specified time (monitored by TLC), the reaction mixture was allowed to cool to room temperature, washed with water (20 mL), and the precipitated selenium power was removed by vacuum filtration. Triethylamine hydrochloride was obtained by evaporation of the aqueous phase. The organic phase was washed with saturated aqueous Na_2CO_3 and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude product which was purified by preparative silica gel TCL using cyclohexane:ethyl acetate (10:1) as eluent.*

VI. NAME REACTIONS

1. The Staudinger Reaction

In the Staudinger reaction, ketenes are generated *in situ* from acid halides by treatment with triethylamine or other tertiary amines and react with imines to produce β-lactams. **BTC** reacts with acids to produce acid chlorides or anhydrides (*see earlier*) and has been successfully employed as an efficient acid activator for the one-step cycloaddition reaction (Staudinger reaction) of acids and imines to β-lactams **125** (*Scheme 71*).[128] This reaction was found to be very



Scheme 71

clean and gave excellent yields of β-lactams. Moreover, this reagent was shown to be better than other acid activators, in terms of yields and simplicity of the work-up procedure.

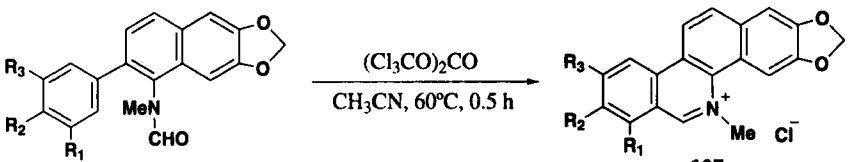
In all the cases, the cycloaddition reaction was stereoselective and only *cis*-β-lactam formation was observed. Therefore, **BTC** was also used as a versatile reagent for the synthesis of β-lactams derived from acids and/or imines which are sensitive to mineral acids or thionyl chloride such as for example the synthesis of β-lactams from the potassium salt of azidoacetic acid or

Dane's salt and various imines and the preparation of β-lactams from imines and chiral acids derived from camphorsultams, oxazolidinones, and carenes.

β-Lactam. General Procedure.-[128] *A solution of triphosgene (0.148 g, 0.5 mmol) in anhydrous CH_2Cl_2 (10 mL) was added slowly to a solution of the acid (1.0 mmol), of the imine (1.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) in anhydrous CH_2Cl_2 (10 mL), at –40°C. The reaction mixture was then allowed to warm up to room temperature and stirred further for 12 h. The reaction mixture was then washed with water (20 mL), saturated sodium bicarbonate solution (2 x 15 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and filtered through a short silica gel column to get the pure β-lactam, which was recrystallized from methanol.*

2. The Bischler-Napieralski Reaction

The use of **BTC** instead of phosphorus oxychloride as a versatile reagent for Bischler-Napieralski reaction has been reported.[129] The Bischler-Napieralski reaction is one of the most important methods for the construction of the isoquinoline ring. Easily handled **BTC** was found to act as an alternative dehydrating reagent of formamide for the formation of the isoquinolines skeleton by BNR of tertiary formamides. Quaternary benzo[*c*]phenanthridines such as the anti-tumor compound nitidine chloride (**127**), were formed directly by cyclization of 2-phenyl-1-(*N*-methylformamido)-naphthalenes **126** with **BTC** at 60°C in acetonitrile (*Scheme 72*).

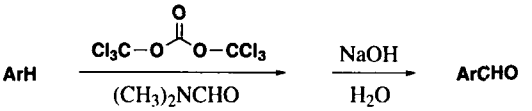


126 **Scheme 72** **127**

Nitidine Chloride. General Procedure.-[129] *A solution of 2-(3',4'-dimethoxyphenyl)-1-(N-methyl-formamido)naphthalene (1 g, 0.278 mmol) and triphosgene (0.18 g, 0.602 mmol) in acetonitrile (2.5 mL) was stirred at 60°C (bath temperature) for 0.5 h. After addition of ice-water, the yellow precipitate was collected and recrystallized from EtOH-ether to give 0.10 g (91%) of nitidine chloride.*

3. The Vilsmeier-Haack Reaction

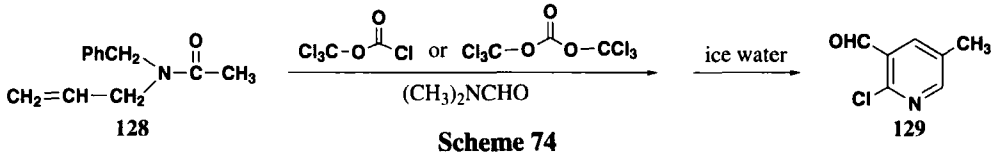
The classical Vilsmeier-Haack reaction is a special case of Friedel-Crafts reaction, involving electrophilic substitution of suitable carbon nucleophiles with the halomethyleni-minium salts, the active intermediates in the Vilsmeier-Haack reaction. In industry, several substituted aldehydes have been prepared by this reaction. Recently, **BTC** (instead of phosphorus oxychloride and phosgene) and dimethylformamide have been used to prepare various aromatic and heteroaromatic aldehydes under mild conditions and in good yields (*Scheme 73*).[130]



a) Ar = *p*-$(CH_3)_2NC_6H_4$; b) Ar = 2-CH_3O-1-$C_{10}H_6$; c) Ar = 2-C_4H_3S; d) Ar = 5-Br-2-C_4H_2S; e) Ar = 2-C_4H_3O; f) Ar = 2-C_4H_4N; g) Ar = N-CH_3-2-C_4H_3N;

Scheme 73

TCF may similarly be employed to prepare aldehydes.[131] 2-Chloro-5-methylpyridine-3-carbaldehyde (**129**), a useful intermediate for a variety of pharmaceutical and pesticide products, was prepared in 92% yield from *N*-benzyl-*N*-(1-propenyl)acetamide (**128**) using diphosgene or triphosgene with DMF as the Vilsmeier-Haack reagent (*Scheme 74*). In addition to avoiding the use of phosgene, the absence of phosphorous salts is also advantageous in industrial applications of **TCF** and **BTC** from the standpoints of safety and environmental acceptability.

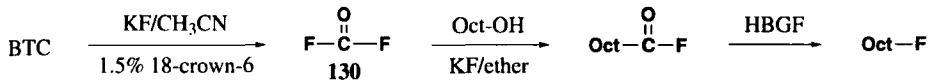


Scheme 74

2-Pyrrolealdehyde. Typical Procedure.-[130] *A flask fitted with a thermometer, an addition funnel, a condenser, and a stirrer was charged with pyrrole (0.13 g, 2.0 mmol) and DMF (2.1 mmol). The flask was immersed in an ice-bath, the stirrer started, and a solution of* ***BTC*** *(0.21 g, 0.7 mmol) in carbon tetrachloride (7 mL), was added over a period of fifteen minutes. The mixture was stirred for 15-30 minutes after the addition. The ice bath was removed and the mixture was heated to 40-50°C for 2 h, then cooled and poured into ice water. The solution was made basic with sodium hydroxide and the layers were separated. The aqueous phase was extracted three times with a total of about 30 mL of ether. The ether and carbon tetrachloride solutions were combined and dried over sodium sulfate. Evaporation of the solvents under reduced pressure gave a residue which was subjected to chromatographic purification on TLC silica gel to give 0.16 g (82%) of 2-pyrrolealdehyde.*

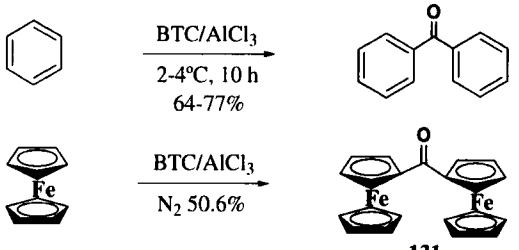
VII. OTHER REACTIONS OF BTC

BTC has been used in some special preparations of organic intermediate compounds such as COF_2, which was obtained from KF and **BTC** in the presence of *18-crown-6*; this was followed by reaction with alcohols to provide alkyl fluorides *via* the alkyl fluoroformates **130** in the presence of catalytic amounts of HBGF (*Scheme 75*).[132]



Scheme 75

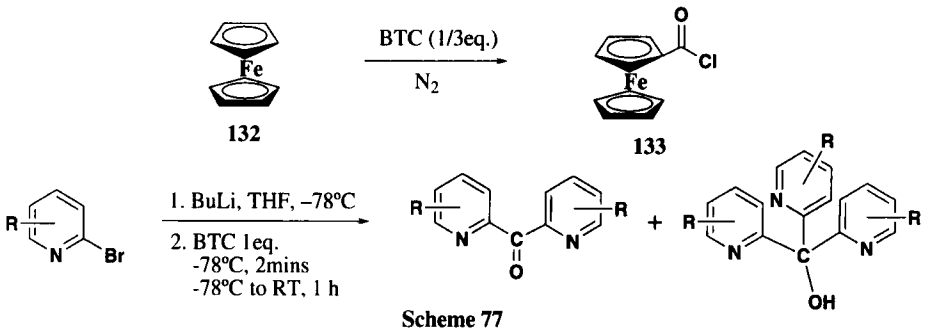
Treatment of **BTC** with aromatic compounds can lead to benzophenones by Friedel-Crafts reaction using $AlCl_3$ as catalyst (*Scheme 76*).[133] Diferrocenoyl (**131**) was synthesized in 51% yield from **BTC** and ferrocene.[134]



131

Scheme 76

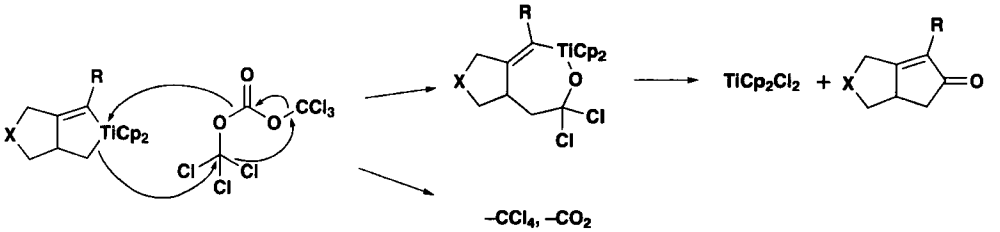
Preparation of ferrocenoyl chlorides (**131**) from ferrocenecarboxylic acid has been previously discussed in the Section on chlorination. Wang *et al.* also reported another method to synthesize ferrocenoyl chlorides from ferrocene (**132**) as starting material. In this reaction, the α-carbon of ferrocene with high partial electron density can act as a nucleophile toward **BTC** to form a C-C bond.[135] Generally, the formation of C-C bond with **BTC** and **TCF** requires a stronger base. Interestingly, Taylor *et al.*[135] reported the formation of C-C bond using a lithium reagent as the nucleophilic species.



132 133

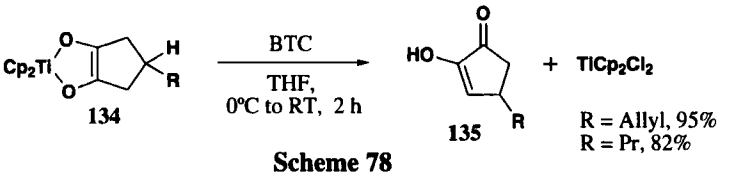
Scheme 77

TCF and **BTC** are also excellent carbonylation agents for the introduction of a carbonyl group, such as in the formation of carbonates, carbamates, ureas and polymers. It has been reported that **BTC** can trap titanacycles leading to bicyclic cyclopentenones *in lieu* of carbon monoxide. A possible mechanism has also been investigated and is shown in *Scheme 78*.[137]



Scheme 78

Carter *et al.* also reported that **BTC** mediates a novel oxidative cleavage reaction, converting the enediolate **134** cleanly to 4-substituted cyclopentane-1,2-diones **135**, which are isolated as the *enol* tautomers (*Scheme 79*).[138]



Scheme 78

VII. CONCLUSION AND OUTLOOK

In summary, **TCF** and **BTC** are very versatile reagents for the preparation of a variety of organic compounds, including chloroformates, isocyanides, isocyanates, isothiocyanates isoselenenocyanates, *N*-carboxyanhydrides (NCA), oxazolidines, polyureas and polycarbonates. Compared with phosgene, both **TCF** and **BTC** are not only safer to use and more conveniently handled, transported and stored but in addition, being a liquid and a solid respectively, they can be weighed exactly. Reactions using these reagents are normally carried out under mild conditions and afford good to excellent yields. **BTC** and **TCF** are widely used in the preparation of medicinal products, pesticides, dyestuffs, paints and the synthetic production of macromolecular materials. We believe that **TCF** and **BTC** will be used even more widely in a variety of applications.

REFERENCES

1. (a) L. Cotarca, P. Delogu, A. Nardelli and V. Sunjic *Synthesis*, 533 (**1996**); (b) H. Eckert and B. Forster, *Angew. Chem. Int. Ed. Engl.*, **26**, 894 (1987); (c) Q. D. You and Q. S. Wang, *Hua Xue Shi Ji*, **14**, 230 (1992); *Chem. Abstr.*, **117**, 250729 (1992).

2. H. Babad and A. G. Zeiler *Chem. Rev.*, **3**, 75 (1973).

3. H. C.Ramsperger and G. Waddington, *J. Am. Chem. Soc.*, **55**, 214 (1933).

4. (a) C. Councler, *Ber.*, **13**, 1697 (1880). (b) H. Eckert and B. Forster, *Angew. Chem. Int. Ed. Engl,*. **26**, 894 (1987).

5. T. Liu, Y. Jiang and Z. Wang, *Hua Xue Shi Ji*, **16**, 381 (1994); *Chem Abstr.*, **122**, 210595 (1994).

6. (a) H. Eckert and B. Forster, *Angew. Chem.*, **99**, 922 (1987); (b) H. Eckert and B. Forster, *Angew. Chem. Int. Ed. Engl.*, **26**, 894 (1987).

7. L. Pasquato, G. Modena, L. Cotarca, P. Delogu and S. Mantovani *J. Org. Chem.*, **65**, 8224 (2000).

8. M. L. Shirel and P. Pulay, *J. Am. Chem. Soc.*, **121**, 8544 (1999).

9. K. Kurita, T. Matsuma and Y. Iwakura, *J. Org. Chem.*, **41**, 2070 (1976).

10. D. Pereira, T. T. Hai and D. Nelson, *Syn. Commun.*, **28**, 4019 (1998).

11. J. I. Lee and H. Park, *Bull. Korean Chem. Soc.*, **22**, 421 (2001); *Chem. Abstr.*, **135**, 137068 (2001).

12. (a) S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981); (b) M. P. Sibi, *Org. Prep. Proced. Int.*, **25**, 15 (1993).

13. O. Unsal and A. Godt., *Chem. Eur. J.*, **5**, 1728 (1999).

14. A. Godt, O. Unsal and V. Enkelmann, *Chem. Eur. J.*, **6**, 3522 (2000).

15. C. Reuter, W. Wienand, G. M. Hubner, C. Seel and F. Vogtle, *Chem. Eur. J.*, **5**, 2692 (1999).

16. F. M. H. de Groot, G. F. Busscher, R. W. M. Aben and H. W. Scheeren, *Bioorg. Med. Chem. Lett.*, **12**, 2371 (2002).

17. R. G. Bhat, E. Kerouredan, E. Porhiel and S. Chandrasekaran, *Tetrahedron Lett.*, **43**, 2467 (2002).

18. S. Beck and H. Koster, *Anal. Chem.*, **62**, 2258 (1990).

19. M. Sawa, Y. Imaeda, J. Hiratake, R. Fujii, R. Umeshita, M. Watanabe, H. Kondo, and J. Oda, *Bioorg. Med. Chem. Lett.*, **8**, 647 (1998).

20. L. J. Wang, H. Y. Li and C. P. Wong, *J. Polym. Sci. Part A: Polym. Chem.*, **38**, 3771 (2000).

21. L. Tang and L. Deng, *J. Am. Chem. Soc.*, **124**, 2870 (2002).

22. D. P. Sahu, *Indian J. Chem.*, **41B**, 1722 (2002).

23. Tanikawa, T. Asaka, M. Kashimura, K. Suzuki, H. Sugiyama, M. Sato, K. Kameo, S. Morimoto and A. Nishida, *J. Med. Chem.*, **46**, 2706 (2003).

24. Q. Cheng, T. Oritani and T. Horiguchi, *Tetrahedron*, **56**, 1667 (2000).

25. S. Zurcher, V. Gramlich, D. V. Arx and A. Togni, *Inorg. Chem.*, **37**, 4015 (1998).

26. H. Mandal and A. S. Hay, *High Perform. Polym.*, **9**, 215 (1997).

27. T. Sugioka and A. S. Hay, *J. Polym. Sci. Part A: Polym. Chem.*, **39**, 1149 (2001).

28. (a) D. Schwinn and W. Bannwarth, *Helv. Chim. Acta,* **85**, 255 (2002); (b) D. Schwinn, H. Glatz and W. Bannwarth, *Helv. Chim. Acta,* **86**, 255 (2003).

29. G. Brooks, W. Burgess, D. Colthurst, J. D. Hinks, E. Hunt, M. J. Pearson, B. Shea, A. K. Takle, J. M. Wilson and G. Woodnutt, *Bioorg. ? Med. Chem.*, **9**, 1221 (2001).

30. S. Sugiyama, K. Morishita and K. Ishii, *Heterocycles,* **55**, 353 (2001).

31. K. Hojo, M. Maeda and K. Kawasaki, *Tetrahedron*, **60**, 1875 (2004).

32. (a) Q. M. Wang and R. Q. Huang, *Tetrahedron Lett.,* **42**, 8881 (2001); (b) Q. M. Wang and R. Q. Huang, *Syn.Commun.,* **34**, 255 (2004).

33. C. H. Xue, Q. M. Mu and S. H. Chen, *Chinese Chem. Lett.,* **12**, 413 (2001); *Chem. Abstr.,* **135**, 227141 (2001).

34. P. L. Wu, C. H. Su and Y. J. Gu, *J. Chinese Chem. Soc.*, **47**, 271 (2000); *Chem. Abstr.,* **122**, 308054 (1995).

35. R. T. Patil, G. Parveen, V. K. Gumaste, B. M. Bhawal and A. R. A. S. Deshmukh, *Synlett,* 1455 (**2002**).

36. A. Jayanthi, V. K. Gumaste and A. R. A. S. Deshmukh, *Synlett,* 979 (**2004**).

37. M. Murakami, Y. Hoshino, H. Ito and Y. Ito, *Chemistry Lett.*, 163 (**1998**).

38. U. M. Joshi, L. N. Patkar and S. Rajappa, *Syn. Commun*, **34**, 33 (2004).

39. L. Tang, Y, S. Yang and R. Y. Ji, *Chinese J. Chem.*, **20**, 1070 (2002); *Chem. Abstr.,* **138**, 255079 (2003).

40. C. J. Lebrun, D. Valognes and S. Halazy, *Syn. Commun*, **28**, 1189 (1998).

41. X. G. Hu, S. M. Wang, Q. X. Zhang, M. M. Cao and Y. Lu, *J. First. Mil. Med. Univ*, **22**, 1042 (2002); *Chem. Abstr.,* **139**, 138503 (2003).

42. G. D. Signore, S. Fioravanti, L. Pellacani and P. A. Tardella, *Tetrahedron*, **57**, 4623 (2001).

43. J. I. Lee and S. J. Park, *Bull. Korean. Chem. Soc.*, **21**, 141 (2000); *Chem. Abstr.,* **132**, 236852 (2000).

44. Z. G. Li, R. Q. Huang and H. Y. Li, *Chinese Chem. Lett.*, **9**, 251 (1998); *Chem. Abstr.,* **131**, 322672 (1999).

45. F. Bachmann, L. Reimer, M. Ruppenstein and J. Thiem, *Macromol. Chem. Phys.*, **202**, 3410 (2001).

46. M. Dudic, P. Lhotak, I. Stibor, K. Lang and P. Proskova, *Org. Lett.*, **5**, 149 (2003).

47. E. J. Warawa, B. M. Migler, C. J. Ohnmacht, A. L. Needles, G. C. Gatos, F. M. Mclaren, C. L. Nelson and M. Kirkland, *J. Med. Chem.*, **44**, 372 (2001).

48. J. M. Huang and R. Y. Chen, *Heteroatom Chem.*, **12**, 97 (2001).

49. P. L. Colla and C. Musiu, *J. Heterocyclic Chem.*, **37**, 1539 (2000).

50. Q. Zhang, C. S. Shi, H. R. Zhang and K. K. Wang, *J. Org. Chem.*, **65**, 7977 (2000).

51. W. Hettrich and R. Becker, *Polymer*, **38**, 2437 (1997).

52. T. E. Edwards, T. M. Okonogi, B. H. Robinson and S. T. Sigurdsson, *J. Am. Chem. Soc.*, **123**, 1527 (2001).

53. F. J. Urban, V. J. Jasys, J. W. Raggon, R. A. Buzon, P. D. Hill and J. D. Weaver, *Syn. Commun.*, **33**, 2029 (2003).

54. H. Boerrigter, L. Grave, J. W. M. Nissink, L. A. J. Chrisstoffels, J. H. V. D. Mass, W. Verboom, F. D. Jong and D. N. Reinhoudt, *J. Org. Chem.*, **63**, 417 (1998).

55. J. A. W. Kruojtzer, D. J. Lefeber and R. M. J. Liskamp, *Tetrahedron Lett.*, **38**, 5335 (1997).

56. C. P. Decicco, J. L. Seng, K. E. Kennedy, M. B. Covington, P. K. Welch, E. C. Arner, R. L. Magolda and D. J. Nelson, *Bioorg. Med. Chem. Lett.*, **7**, 2331 (1997).

57. J. Szadowski, Z. Nieoviaclomski and K. Wojciechowski, *Dyes and Pigments*, **50**, 87 (2001).

58. I. Maya, O. Lopez, S. Maza, J. G. F. Bolanos and J. Fuentes, *Tetrahedron Lett.*, **44**, 8539 (2003).

59. A. D. Stefano, B. Mosciatti, G. M. Cingolani, G. Giorgioni, M. Ricciutelli, I. Cacciatore, P. Sozio and F. Claudi, *Bio. Med. Chem. Lett.*, **11**, 1085 (2001).

60. K. T. Huang and C. M. Sun, *Bioorg. Med. Chem. Lett.*, **11**, 271 (2001).

61. V. K. Potluri and A. D. Hamilton, *J. Supramolecular Chem.*, **2**, 321 (2002).

62. Q. W. Wang, Z. G. Li, R. Q. Huang and J. R. Cheng, *Heteroatom Chem.*, **12**, 68 (2001).

63. S. Yagi, I. Yonekura, M. Awakura, M. Ezoe and T. Takagishi, *Chem. Commun.*, 557 (**2001**).

64. M. Dudic, P. Lhotak, I. Stibor, K. Lang and P. Proskova, *Org. Lett.*, **5**, 149 (2003).

65. L. Michaudet, P. Richard and B. Boitrel, *Tetrahedron Lett.*, **41**, 8289 (2000).

66. J. P. Collman, Z. Wang and A. Straumanis, *J. Org. Chem.*, **63**, 2424 (1998).

67. M. Alvarez, D. Fernandez and J. A. Joule, *Tetrahedron Lett.*, **42**, 315 (2001).

68. S. Fustero, E. Salavert, J. F. S. Cervera, J. Piera and A. Asensio, *Chem. Commun.*, 844 (**2003**).

69. J. D. Garcia, R. Somanathan, I. A. Rivero, G. Aguirre and L. H. Hellberg, *Syn. Commun.*, **30**, 2707 (2000).

70. D. Ranganathan and C. Lakshmi, *Chem. Commun.*, 1250 (**2001**).

71. Q. M. Wang, J. R. Cheng and R. Q. Huang, *J. Heterocyclic Chem.*, **40**, 195 (2003).

72. Z. F. Li and Y. M. Zhang, *Syn. Commun.*, **32**, 2613 (2002).

73. C. Songkram, R. Yamasaki, A. Tanatani, K. Takaishi, K. Yamaguchi, H. Kagechika and Y. Endo, *Tetrahedron Lett.*, **42**, 5913 (2001).

74. (a) M. J. Coghlan and B. A. Caley, *Tetrahedron Lett.*, **30**, 2033(1989); (b) R. Wilder and S. Mobashery, *J. Org. Chem.*, **57**, 2755 (1992).

75. (a) F. Cornille and M. Lebon, US 6,603,016; *Chem. Abstr.*, **137**, 385110 (2002); (b) H. Lin, Z. Z.Shao, P. Zhou, Q. W. Gao, T. Y. Yu, *Gaodeng Xuexiao Huaxue Xuebao*, **21**, 819 (2000); *Chem. Abstr.*, **133**, 105645 (2000).

76. I. A. Rivero, S. Heredia and A. Ochoa, *Syn. Commun.*, **31**, 2169 (2001).

77. G. L. Zhang, P. Zhang, Y. G. Yang, C. J. Tang, D. Ye, X. S. Bai, H. Xie, *Faming Zhuanli Shenqing Gongkai Shuomingshu* CN 1289779 A 4; *Chem. Abstr.*, **136**, 6341 (2002).

78. N. Higashi, T. Koga and M. Niwa, *Langmuir*, **16**, 3482 (2000).

79. M. Mabuchi, S. Kobata, S. Ito, and M. Yamamoto, *Langmuir*, **14**, 7260 (1998).

80. H. Lin, Z. Z. Shao, P. Zhou, Q. W. Gao and T. Y. Yu, *Chem. J. Chinese Univ.*, **5**, 819 (2000); *Chem. Abstr.*, **133**, 105645 (2000).

81. B. Thern, J. Rudolph and G. Jung, *Tetrahedron Lett.*, **43**, 5013 (2002).

82. C. L. Gibson, K. Gillon and S. Cook, *Tetrahedron Lett.*, **39**, 6733 (1998).

83. M. Kluge and D. Sicker, *J. Nat. Prod.*, **61**, 821 (1998).

84. T. Izuhara and T. Katoh, *Org. Lett.*, **3**, 1653 (2001).

85. T. Subramanian, C. C. Lin and C. C. Lin, *Tetrahedron Lett.*, **42**, 4079 (2001).

86. M. Catasús, A. Moyano, and V. K. Aggarwal, *Tetrahedron Lett.*, **43**, 3475 (2002).

87. M. Catasús, A. Bueno, A. Moyano, M. A. Maestro and J. Mahía, *J. Organometallic Chem.*, **642**, 212 (2002).

88. D. Cabaret, M. G. Gonzalez, M. Wakselman, S. A. Adediran and R. F. Pratt, *Eur. J. Org. Chem.*, 141 (**2001**).

89. H. Kagoshima and K. Shimada, *Chemistry Lett.*, **32**, 514 (2003).

90. (a) B. Noya, M. D. Paredes, L. Ozores and A. Aloneo, *J. Org. Chem.*, **65**, 5960 (2000); (b) K. K. Lindsay and S. G. Pyne, *Synlett*, **5**, 779 (2004).

91. H, Z. Alkhathlan, *Tetrahedron*, **59**, 8163 (2003).

92. H, Z. Alkhathlan, *Syn. Commun.*, **43**, 71 (2004).

93. H, Z. Alkhathlan, *Tetrahedron*, **59**, 8163 (2003).

94. B. Wang, X. M. Yu and G. Q. Lin, *Synlett*, 904 (**2001**).

95. M. B. Choyussy, S. Cadet, M. D. Paolis and J. Zhu, *Tetrahedron Lett.*, **42**, 4503 (2001).

96. Y. Matsushima, T. Nakayama, S. Tohyama, T. Eguchi and K. Kakinuma, *J. Chem. Soc., Perkin Trans. 1*, 569 (**2001**).

97. F. Chau, J. C. Malanda and R. Milcent, *J. Heterocyclic Chem.*, **43**, 1603.

98. F. E. Dayan, G. Meazza, F. Bettarini. E. Signorini, P. Piccardi, J. G. Romagni and S. O. Duke, *J. Agric. Food Chem.*, **49**, 2302 (2001).

99. C. B. Vicentini, G. Forlani, M. Manfrini, C. Romagnoli and D. Mares, *J. Agric. Food Chem.*, **50**, 4839 (2002).

100. F. E. Dayan, G. Meazza, F. Bettarini. E. Signorini, P. Piccardi, J. G. Romagni and S. O. Duke, *J. Agric. Food Chem.*, **49**, 2302 (2001).

101. Q. M. Wang and R. Q. Huang, *J. Organometalic Chem.*, **604**, 287 (2000).

102. (a) W. Bao and Q. Wang, *J. Chem. Res.(S)*,**11**,700 (2003); (b) V. K. Gumaste, B. M. Bhawal and A. R. A. S. Deshmukh, *Tetrahedron Lett.*, **43**, 1345 (2002).

103. I. A. Rivero, S. Heredia and A. Ochoa, *Syn. Commun.*, **31**, 2169 (2001).

104. R. M. Cicchillo and P. Norris, *Carbohydrate Res.*, **328**, 431 (2000).

105. L. M. Hu, Z. J. Liu and G. Yan, *Hunan Huagong*, **30**, 15 (2000); *Chem. Abstr.*, **135**, 7114 (2001).

106. (a) P. Li and J. C. Xu, *Chemistry Lett.*, 1163 (**1999**); (b) E. H. Wang and W. G. Wu, *J. China Pharm. Univ.*, **32**, 245 (2001); *Chem. Abstr.*, **137**, 109256 (2002).

107. D. A. Flosser and R. A. Olofson, *Syn. Commun.*, **33**, 2045 (2003).

108. L. Dahlenburg and A. Kaunert, *Eur. J. Inorg. Chem.*, 885 (**1998**).

109. E. Lindner, M. Schmid, J. Wald, J. A. Queisser, M. Geprägs, P. Wegner and C. Nachtigal, *J. Organometallic Chem.*, **602**, 173 (2000).

110. (a) W. K. Su, X. R. Liang, Y. S. Li and Y. M. Zhang, *Chinese J. Org. Chem.*, **9**, 1019 (2003); *Chem. Abstr.*, **140**, 110822 (2004); (b) Y.S. Li, X.R. L. Liang and W. K. Su, *Org. Prep. Proced. Int.* **35**, 613 (2003).

111. (a) A. K. Ghosh, T. T. Dugong and S. P. Mckee, *Tetrahedron Lett.*, **32**, 4251 (1991); (b) D. P. Sahu, *Indian J. Chem. Sect. B.*, **32**, 385(1993); (c) K.Mai and G. Patil *Tetrahedron Lett.*, **27**, 2203 (1986).

112. D. S. Bose and P. R. Goud, *Syn. Commun.*, **32**, 3621 (2002).

113. D. Lentz, *Angew. Chem.*, **106**, 1377 (1994); *Angew. Chem. Int. Ed. Engl.*, **33**, 927 (1994).

114. J. C. A. Boeyens, L. M. Cook, Y. Ding, M. A. Fernandes and D. H. Reid, *Org. Biomol. Chem.*, **1**, 2168 (2003).

115. D. W. Price and T. M. James, *Tetrahedron*, **59**, 3131 (2003).

116. P. Ilankuymaran, P. Kisanga and J. G. Verkade, *Heteroatom Chem.*, **12**, 561 (2001).

117. J. R. Simon and R. Neidlein, *Synthesis*, 1101 (**2000**).

118. F. E. Haln, V. Langenhahn, N. Meier, T. Lügger and W. P. Fenlhammer, *Chem. Eur. Lett.*, **9**, 704 (2003).

119. S. Marcaccini and T. Torroba, *Org. Prep. Proced. Int.*, **25**, 141 (1993).

120. B. Henkel, B. Beck, B. Westner, B. Mejat and A. Domling, *Tetrahedron Lett.*, **44**, 8947 (2003).

121. P. Ilankuymaran, P. Kisanga and J. G. Verkade, *Heteroatom. Chem.*, **12**, 561 (2001) .

122. (a) N. Petragnam, A. Stefani and C. J. Valduga, *Tetrahedron*, **57**, 1411 (2001); (b) B. D. Johnston, A. Ghavami, M. T. Jensen, B. Svensson and B. M. Pinto, *J. Am. Chem. Soc.*, **124**, 8245 (2002).

123. D. H. R. Barton, S. I. Parekh, M. Tajbakhsh, E. A. Theodorakis and C. L. Tse, *Tetrahedron*, **50**, 639 (1994).

124. W. K. Su and X. R. Liang, *J. Indian Chem. Soc.*, **80**, 645 (2003).

125. J. G. F. Bolaños, Ó. López, V. Ulgar, I. Maya and J. Fuentes, *Tetrahedron Lett.*, **57**, 1411 (2001).

126. A. K. Mukerjee and R. Ashare, *Chem. Rev.*, **91**, 1 (1991).

127. W. G. Shan. G. F. Bian. W. K. Su and X. R. Liang, *Org. Prep. Proced. Int.*, **36**, 284 (2004).

128. (a) D. Krishnaswamy, B. M. Bhawal and A. R. A. S. Deshmukh, *Tetrahedron Lett.*, **41**, 417(2000); (b) D. Krishnaswamy, V. V. Govande, V. K. Gumaste, B. M. Bhawal and A. R. A. S. Deshmukh, *Tetrahedron*, **58**, 2215 (2002).

129. T. Saito, M. Yoshida and T. Ishikawa, *Heterocycles*, **54**, 437 (2001).

130. W. G. Shan, X. J. Shi and W. K. Su, *Org. Prep. Proced. Int.*, **36**, 337 (2004).

131. G. Banda, C. Bhimapaka and V. J. Rao, *US 6,479,664 B1*; *Chem. Abstr.*, **137**, 352892 (2002).

132. D. A. Flosser and R. A. Olofson, *Tetrahedron Lett.*, **43**, 4275 (2002).

133. X. Peng, J. Wang, J. Cui, R. Zhang and Y. Yan, *Syn. Commun.*, **32**, 2361 (2002).

134. Q. M. Wang and R. Q. Huang, *J. Organometalic Chem.*, **604**, 287 (2000).

135. M. J. Hannon, P. C. Mayers and P. C. Taylor, *Tetrahedron Lett.*, **39**, 8509 (1998).

136. (a) Z. B. Zhao and Y. Ding, *J. Chem., Perkin Trans. 1*, 171 (**1998**); (b) T. Imakubo, H. Sawa and R. Kato, *Syn. Metals*, **86**, 1883 (1998).

137. Z. B. Zhao, Y. Ding and G. Zhang, *J. Org. Chem.*, **63**, 9286 (1998).

138. C. A. G. Carter, G. L. Casty and J. M. Stryker, *Synlett*, 1046 (**2001**).

(Received September 30, 2004; in final form November 12, 2004)