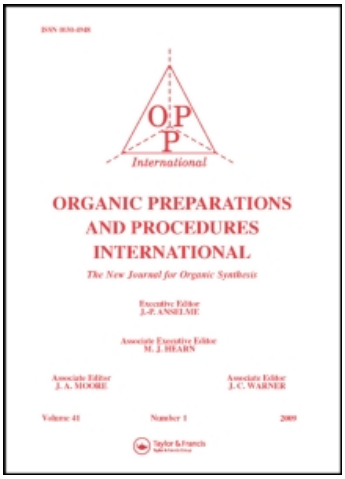

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Recent Developments in the Use of *bis*-(Trichloromethyl) Carbonate in Synthesis

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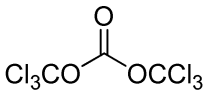
Introduction

As a significant substitute for the traditional chlorination reagents such as $POCl_3$, $SOCl_2$, phosgene, trichloromethyl chloroformate (TCF, diphosgene), *bis*-(trichloromethyl) carbonate (BTC, triphosgene, **1**) is safer and more convenient to handle, transport, and store. Its physicochemical properties have been described in previous reviews.[1,2] Recently, BTC played indispensable roles in the synthesis of important classes of organic compounds, as well as contributing significantly to reducing environmental pollution in the future. So far, BTC has been employed in various aspects of organic synthesis such as chlorination, acylation, cyclizations, ring-opening reactions, Vilsmeier reactions and dehydration reactions, *etc.*[1, 2]



(BTC, triphosgene 1)

Scheme 1

BTC can react with various nucleophiles, and the reactions with BTC are of great interest for their unique reactivity, selectivity, and mild reaction conditions. The diversity of the new structures obtained by these reactions means that BTC has particular importance as a valuable reagent in the preparation of various organic compounds, and its use can result in the highly efficient synthesis of a variety of compounds: chlorocarbonyl derivatives, isocyanates, *N,N*'-disubstituted(poly)ureas, (poly)carbonates, alkyl and acyl chlorides, and

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heterocyclic compounds.[1,2] The following figure shows that the synthetic applications of BTC has been growing from 1996 to 2007 (*Figure 1*).

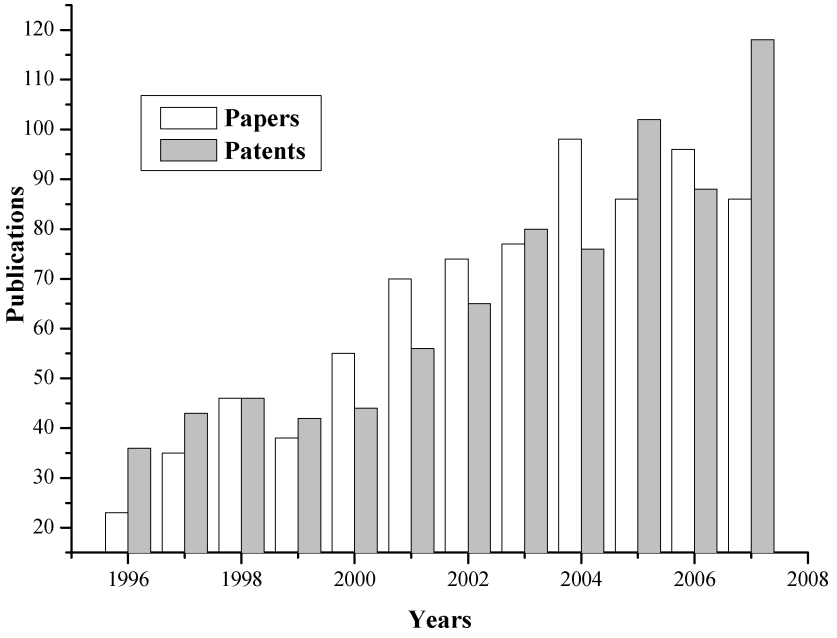


Figure 1. Number of papers and patents on BTC.

Up to now, there have been two reviews about significant contributions on BTC, in 1995[1] and 2004.[2] Ever since then, there have been more and more reports about BTC both in its applications and reaction-type in the publications of the past five years, from 2004 to 2008. Recently, reactions utilizing the Vilsmeier reagent derived from BTC/DMF have attracted considerable attention. In comparison with the traditional Vilsmeier reagent derived from $POCl_3$/DMF, studies carried out indicate that Vilsmeier reagent generated *in situ* from BTC and DMF provides good selectivity, higher yields, and avoids the formation of inorganic phosphorus salts. We believe this Vilsmeier reagent will bring more practical applications in the future. In addition, BTC has increasingly been employed in the synthesis of a large number of compounds with high biological activities such as quinoxalinones,[3] 1,3,4-benzotriazepines derivatives,[4,5] *N*-alkenylbenzimidazol-2-ones,[6] and oxazinones.[7] Although more than a century old compound, the continuous growing interests show that BTC is also a versatile synthetic auxiliary with extensive applications in the synthesis of some important classes of organic compounds. This review aims to give an overview of the latest advances of BTC in organic synthesis from 2004 to 2008.

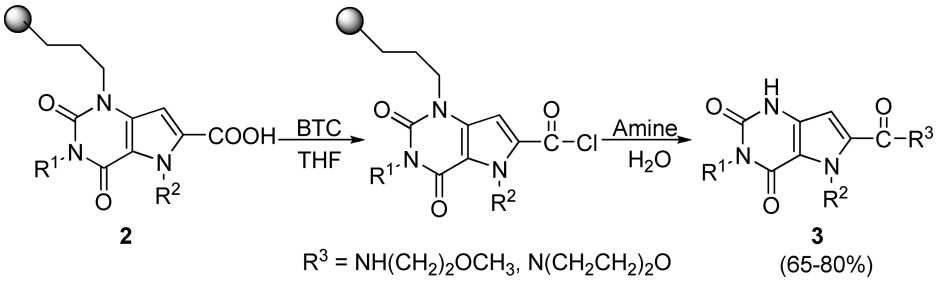
I. Chlorination

1. Chlorination of Hydroxy Groups

a. Synthesis of Acid Chlorides

Acid chlorides are important intermediates in synthesis of many classic compounds. Fridkin *et al.*[8] presented an effective method for the solid-phase preparation of

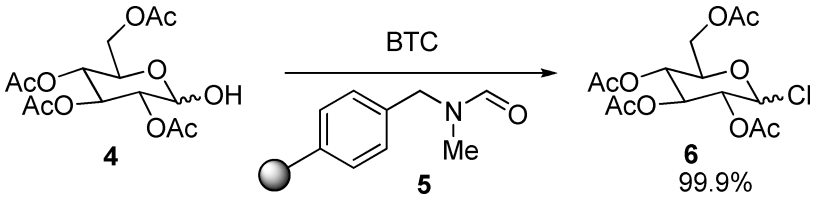
pyrrolo[3,2-*d*]pyrimidine-6-carboxamides **3** from pyrrolo[3,2-*d*]pyrimidine-6-carboxylic acids 2. In this reaction (*Scheme 2*), activation of resin-bound carboxylic acids was performed by *in situ* conversion to their acid chlorides using 33 mol % of BTC in the presence of 900 mol % of collidine as base for 2 min at room temperature. High coupling yields were ensured by repeating the coupling procedure once more after resin washings, utilizing the same conditions. The most interesting point in this reaction is that the ultimate product of pyrrolo[3,2-d]pyrimidine-6-carboxamides can be easily separated in reasonably high purity of 65–80% from the solid support without any further treatment.



Scheme 2

b. Synthesis of Alkyl Chlorides

Glycosyl chlorides **6** (*Scheme 3*) are employed to synthesize complex *O*-glycosides in the presence of heavy metal salts or halide ions as promoters.[9] The original route used BTC or oxalyl chloride as a chlorinating reagent for the preparation of glycosyl chlorides **6** from sugar hemiacetals **4** in the presence of DMF. Herein, BTC is known to react with DMF under mild conditions to generate the corresponding Vilsmeier salt.[10–12] Chiara *et al.*[9] provided a wonderful method which used BTC as the chlorinating reagent in combination with the resin-bound formamide **5** to give very high yields of the desired chlorides. (>99% yield in each case).[13]

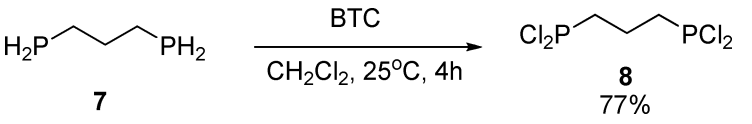


Scheme 3

2. Chlorination of RPH_2 and $P(OR)_3$

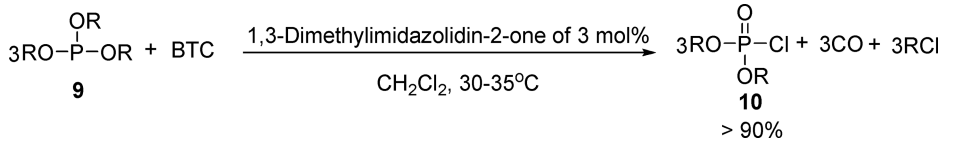
Phosgene and diphosgene (TCF) have been utilized in the chlorination of RPH_2. Recently Susan *et al.*[14] reported that 1,3-*bis*(dichlorophosphino)propane **8** was conveniently prepared in high yield when **BTC** was treated with 1,3-diphosphinopropane 7 in dichloromethane

(*Scheme 4*). In this case, it provided a clean alternative, higher yield, and BTC is more efficacious and considerably less toxic than phosgene in this reaction.



Scheme 4

Dialkyl chlorophosphates have been used in synthesis of phosphorus-based insecticides/ pesticides and as intermediates for the transformation of many types of compounds such as fungicides, retardants, lubricants, phosphoramidates, phosphates, enolphosphates, and phosphorohydrazides.[15] A mild and simple method for the synthesis of dialkyl chlorophosphates **10** is described,[15] where BTC is used as an effective reagent for the conversion of trialkyl phosphites **9** to the corresponding dialkyl chlorophosphates **10** under mild conditions (*Scheme 5*). Cotarca *et al.*[16] reported that Ph_3P/BTC is a better chloride reagent than Ph_3P/CCl_4 and Ph_3P/hexachloreacetone, which allows complete chlorination of alcohols. Su *et al.*[17,18] 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.



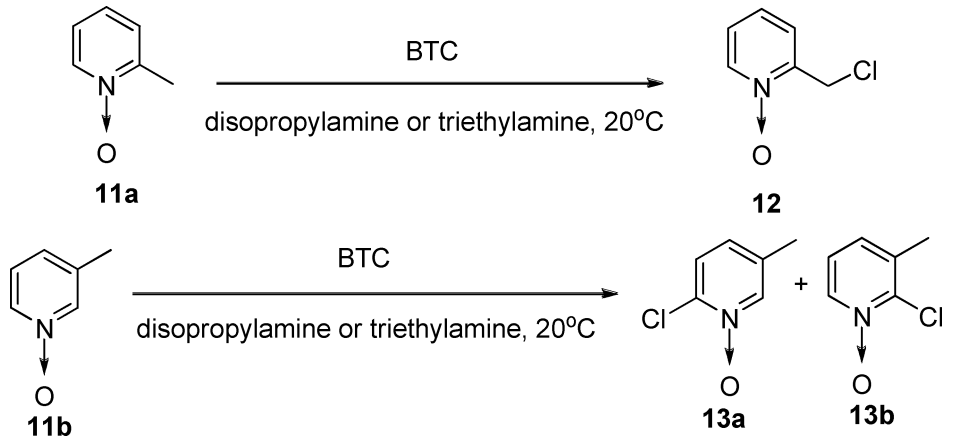
Scheme 5

3. Chlorination of C-H Bonds

Chloromethylpyridines and chloropyridines constitute an important class of compounds in the preparation of pharmaceuticals, dyes, and pesticides.[28] The original methods for the preparation of chloromethylpyridines and chloropyridines involve the chlorination of picolines[19] and pyridine *N*-oxides[20, 21] with reagents such as $POCl_3$,[22, 23] SO_2Cl_2,[24] phosgene in DMF,[25] trichloroacetyl chloride,[26] or sulfonyl chlorides.[27] Rao *et al.*[28] reported that BTC in the presence of amines was found to be an excellent chlorinating agent with high selectivity for the preparation of chloromethylpyridines **12** and chloropyridines **13** from picoline *N*-oxides **11a** and **11b** respectively. The reaction using disopropylamine/Et_3N as bases proceeded in very good yields (*Scheme 6 and Table 1*).

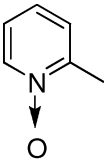
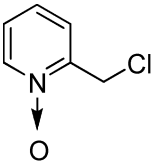
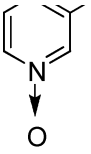
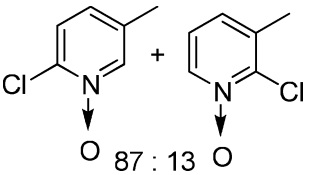
4. Chlorination of Ketones

Compared to the chlorinating agents such as $SOCl_2$ or PCl_3, BTC is a safer and more effective agent for the chlorination of ketones. Our group[29] reported that *via* a catalytic cycle in the presence of scandium triflate (2 mol%)/DMF (1 mol%)/benzoyl chloride (5 mol %), aromatic ketones were treated with BTC to afford aryl-(Z)-vinyl chlorides **14** (*Scheme 7*). In this reaction, DMF is a base and catalyst for the preparation of benzoyl

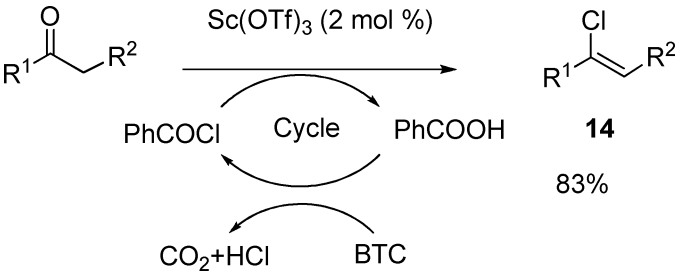


Scheme 6

Table 1
Facile and Selective Synthesis of Chloromethylpyridines and Chloropyridines

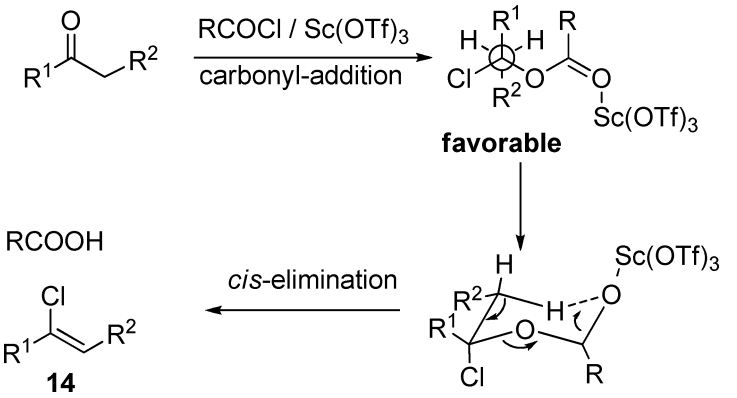
Substrate	Reagent	Product	Temperature (°C)	Yield[a] (%)	Yield[b] (%)
	BTC		−20	90	88
	BTC	 87 : 13	−20	80	78

a) Disopropylamine as base; b) Et_3N as base.



Scheme 7

chloride. Various metal triflates tested in the reaction showed high catalytic activity. A plausible addition-elimination mechanism was proposed (*Scheme 8*).



Scheme 8

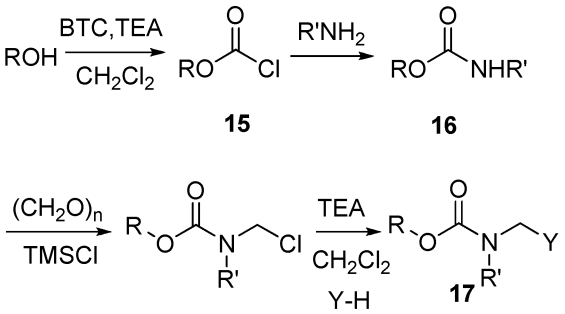
II. Acylation

1. Acylation of Hydroxy and Sulfhydryl Groups

Acylation of alcohols or thiols with BTC provides the corresponding chloroformates readily. However, most of the chloroformates are unstable and difficult to isolate. They can react with a second nucleophile forming more stable products such as carbonates, carbamates, *etc*.

a. Preparation of Chloroformates

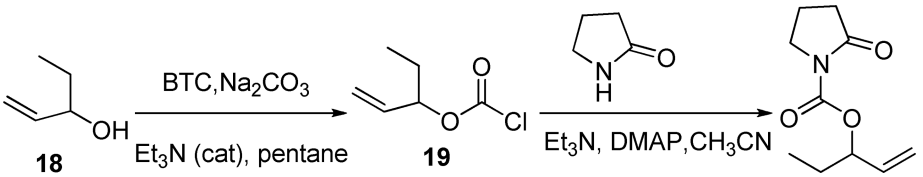
N-Alkyl-*N*-alkyloxycarbonylaminomethyl derivatives **17** can be classed as soft alkyl prodrugs. Firstly, acylation of an alcohol with BTC yielded chloroformate **15**, followed by the addition of alkylamine to afford N-alkylcarbamic acid alkyl ester **16**. Then, compounds **17** can be obtained by alkylation of *N*-Alkyl-*N*-alkyloxycarbonylaminomethyl chlorides in good yields (*Scheme 9*).[30]



R = propyl, butyl, hexyl; R' = methyl, propyl, *n*-butyl; Y = acetaminophen (APAP), 6-mercaptopurine (6MP) or theophylline (Th), TEA = triethylamine.

Scheme 9

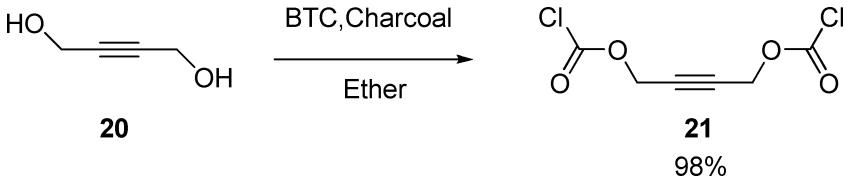
Recently, Martin *et al.*[31] reported a simple method for the preparation of 1-ethylallyl chloroformate **19** which was shown to be a novel carbamates protecting reagent for secondary amines and amides. Furthermore, the protecting group could be cleaved under mild conditions catalyzed by $Pd(PPh_3)_4$. 1-Ethylallyl chloroformate **19** was prepared from pen-1-en-3-ol **18** in pentane by treating with BTC at 0°C (*Scheme 10*).



Scheme 10

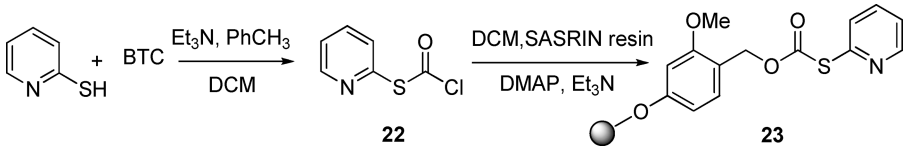
1-Ethylallyl Chloroformate 19. Typical Procedure.[31] *Et_3N (21 μL, 0.15 mmol) was added to a solution of triphosgene (328 mg, 1.10 mmol) and Na_2CO_3 (318 mg, 3.0 mmol) in pentane (5 mL) at 0°C, and the mixture was stirred for 30 min. A solution of pent-1-en-3-ol **18** (308 μL, 3.0 mmol) in pentane (5 mL) was added dropwise at 0°C, the mixture was allowed to warm to 25°C, and stirring was continued for 16 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give 445 mg (99%) of 1-ethylallyl chloroformate **19** as a clear oil.*

But-2-ynyl-*bis*-oxycarbonyl chloride (BbcCl, **21**) was the first C_2-symmetric protecting reagent for amines and amino acids. Chandrasekaran *et al.*[32] reported a method for the preparation of **21** using BTC and but-2-yne-1,4-diol **20** (*Scheme 11*). Moreover, compound **21** has been commonly applied to peptide synthesis.[32]



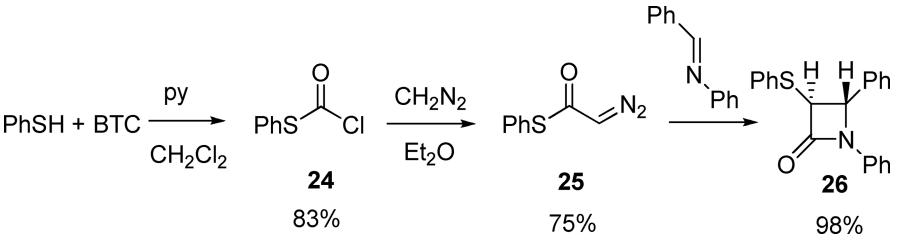
Scheme 11

Recently, Zhang *et al.*[34] reported a synthetic method for the preparation of SASRIN–TOPCAT resin **23** which can be more suitable for the loading of alcohols in solid-phase organic synthesis. Firstly, 2-thiopyridyl chloroformate **22** was obtained by reacting with BTC, followed by addition of SASRIN resin (Super Acid Sensitive Resin)[33] to give SASRIN–TOPCAT resin **23** (*Scheme 12*).



Scheme 12

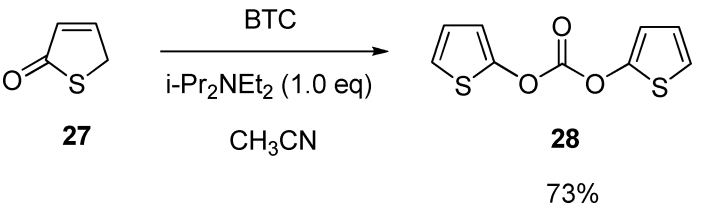
3-Phenylthio β-lactam derivatives such as **26** are very useful synthetic intermediates. The previous methods for the synthesis of 3-phenylthio β-lactam derivatives usually involved the 2-phenylthioacetic acid derivative/Et_3N/imine system.[35] However, these methodologies were associated with one or more disadvantages, such as relative long reaction time, high cost, low yield, inconvenient procedure, or harsh reaction conditions.[7] Zhang *et al.*[36] reported the synthesis of 3-phenylthio β-lactam **26** by a three-step process. Treatment of thiophenol with BTC afforded the phenyl chlorothioformate **24**, followed by reacting with diazomethane in a diethyl ether solution to give the desired α-diazo thiol ester **25**. Then, treatment of **25** with imines produced the desired 3-phenylthio β-lactam **26** in good yield (*Scheme 13*). The main advantages of this route are more convenient procedure, short reaction time, good yield, and without the use of the expensive catalyst.



Scheme 13

b. Preparation of Carbonates

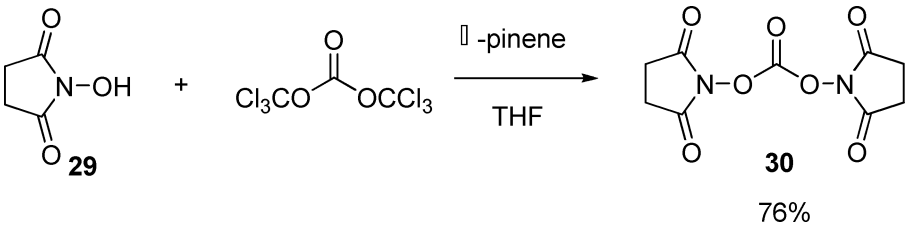
BTC is a convenient reagent for the introduction of the carbonate moiety. Symmetrical carbonates are well-known compounds and can be used as coupling agents.[37] For example, di-2-thienylcarbonate (2-DTC) **28** is a stable crystalline compound, and can be stored under argon at room temperature for over one month without any decomposition. Mukaiyama *et al.*[38] have reported an improved method for preparation of 2-DTC **28** from BTC and 2(5*H*)-thiophenone in good yields (*Scheme 14*).



Scheme 14

Di-2-Thienyl Carbonate (2-DTC) 28. Typical Procedure.[38] *After a mixture of 2(5H)-thiophenone 27 (100 mg, 1.0 mmol) and i-Pr_2NEt_2 (0.174 mL, 1.0 mmol) in CH_3CN (3 mL) had been stirred for 10 min at room temperature under an argon atmosphere, triphosgene (49.6 mg, 0.167 mmol) in CH_3CN (1 mL) was added at -50^oC, and the reaction mixture was stirred for 2 h at -50^oC. After evaporation of the solvent, the residue was dissolved in ether and filtered. After evaporation of the solvent, the residue was separated by short silica-gel column chromatography (eluent: hexane/AcOEt = 12/1) and recrystallized from 2-propanol to afford 2-DTC **28** (82.4 mg, 73%) as a colorless solid.*

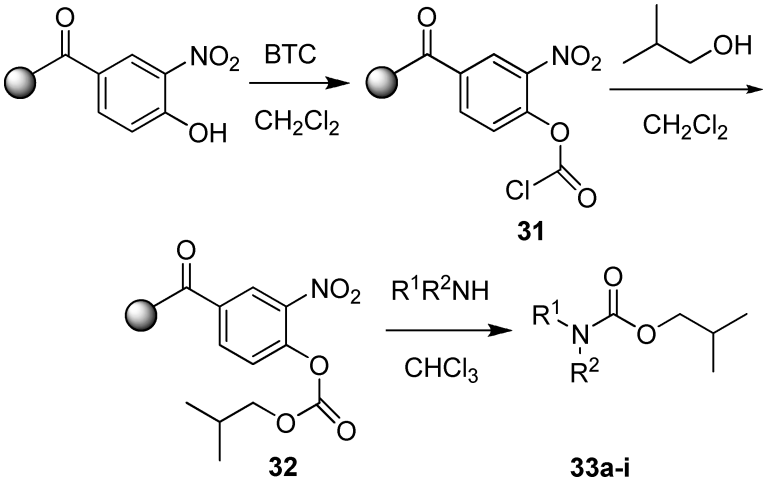
N,N-Disuccinimidyl carbonate (DSC) **30** can be utilized in many synthetic applications because of its stability. Prasad *et al.*[40] reported an improved method for synthesis of DSC in high yield using α-pinene as an acid scavenger. Primary and secondary amines cannot be used as acid scavengers because they are able to react with BTC.[39] Tertiary amines cannot be used because their hydrochloride salts are insoluble in organic solvents, and it is difficult to separate the salts from DSC. Only complex and expensive tertiary amines such as tributyl amine[37] were used to obtain the pure product. Herein, α-pinene is inexpensive and readily available (*Scheme 15*).



Scheme 15

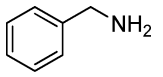
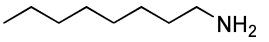
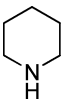
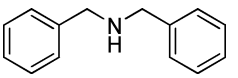
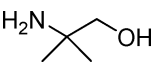
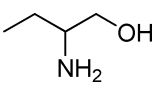
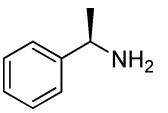
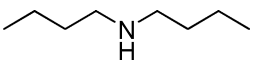
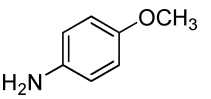
Unsymmetrical carbonates have very wide applications in chemistry, for example, in the design and synthesis of various prodrugs, peptide and protein synthesis, chemiluminescence assays, and underfill technology.

Carbamates such as **33** are widespread functional groups in organic synthesis, and can be used as protecting groups for the amino function especially in the chemistry of peptides and peptidomimetics.[41] Treatment of nitrophenyl resin with BTC afforded the chloroformate **31**, followed by reacting with isobutyl alcohol under mild conditions to give the intermediate carbonate **32**. Then, treatment of amines produced the desired carbamates **33** in good yield (*Scheme 16*).[42] In addition, the nitrophenyl resin can be reused with no significant loss of efficiency.

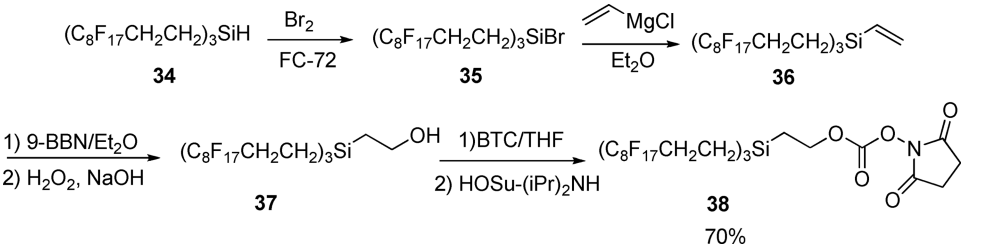


Scheme 16

Table 2
Synthesis of Carbamates from Different Amines

Entry	Amine	Carbamate	Yiled (%)
1		**33a**	88
2		**33b**	75
3		**33c**	89
4		**33d**	69
5		**33e**	99
6		**33f**	94
7		**33g**	81
8		**33h**	88
9		**33i**	40

2-[tris(Perfluorodecyl)silyl]ethoxycarbonyl-*O*-succinimide **38** has been employed as a new fluorous protecting agent. Takeuchi *et al.*[45] reported a method for synthesis of Binstratamide H, known to possess potent pharmacological activities,[43, 44] using this new fluorous protecting agent. In addition, the fluorous protecting group can be removed from Binstratamide H and the recovered fluorous fragment is demonstrated to be recycled by using vinyl magnesium chloride. Fluorous hydrosilane **34** was first treated with bromine to yield the corresponding silylbromide **35**, followed by the addition of vinyl-magnesium chloride to afford vinylsilane **36**. Then the viylsilane **36** was reacted sequentially with 9-borabicyclo[3,3,1] nonane (9-BBN) and hydrogen peroxide to give fluorous silylethanol

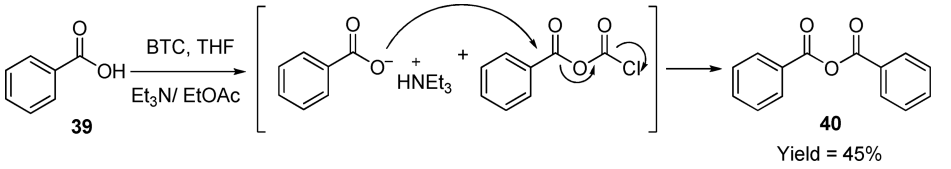


Scheme 17

37. In the final step, the silylethanol **37** was reacted with BTC and N-hydroxysuccimide to give the fluorous protecting agent **38**. The overall yield from the hydrosilane **34** was about 70% (*Scheme 17*).

c. Preparation of Acid Anhydrides

Carboxylic acid anhydrides can be prepared from carboxylic acids and BTC. For example, benzoic anhydride **40** can be easily synthesized by treating benzoic acid **39** and BTC in mild conditions (*Scheme 18*).[46]



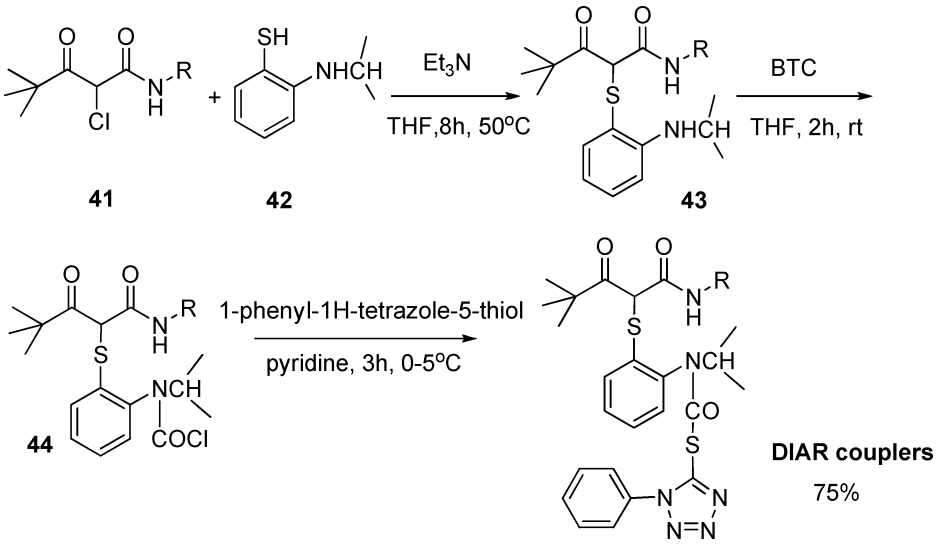
Scheme 18

2. Acylation of Amines

a. Preparation of Carbamoyl Chlorides

Carbamoyl chlorides are functional intermediates which can be used in the synthesis of a wide range of carbamates, ureas, or heterocyclic derivatives by treatment of the corresponding amine with BTC.[47–53] Extensive work has generated many new synthetic applications of carbamoyl chlorides.

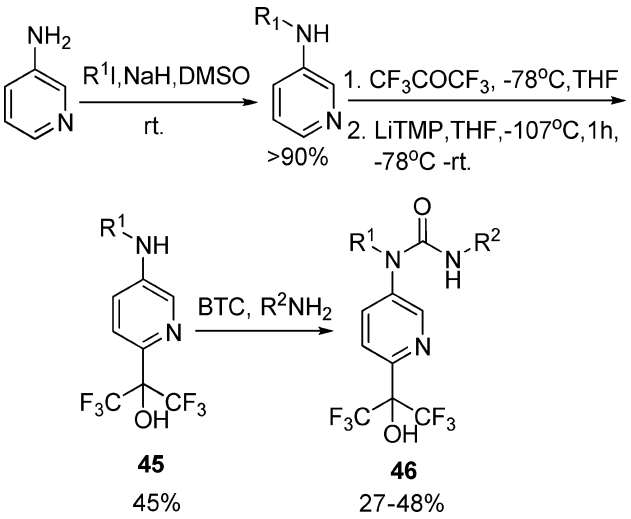
Lu and co-workers[54] reported the synthesis and characterization of some novel photographic DIAR (Development Inhibitor Archimeric Releasing) couplers. The couplers' intermediates **44** were prepared by a modified method using BTC as a chloroformylation reagent, in place of phosgene, in good yield. The results are shown in *Scheme 19*.



Scheme 19

Compound 44. Typical Procedure.[54] *A solution of* BTC *(1.5 g, 0.005 mol) in tetrahydrofuran (5 ml) was added dropwise into a solution of compound* ***43*** *(7.3 g, 0.01 mol) and dimethylaniline (1.22 g, 0.01 mol) in tetrahydrofuran (20 ml) at 0°C. After addition, the reaction mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the solid product compound* ***44*** *was obtained.*

In 2006, Cheng's group[55] reported a synthetic method of heteroaryl-substituted bis-trifluoromethyl carbinols used as malonyl-CoA decarboxylase (MCD) inhibitors for the treatment of certain disorders involving fatty acid/glucose metabolism. One route to the target compounds **46** is outlined in *Scheme 20*. Treatment of intermediates **45** with BTC provided the carbamoyl chloride intermediates, which without further purification were reacted with a primary or secondary amine to afford the desired derivatives **46**.



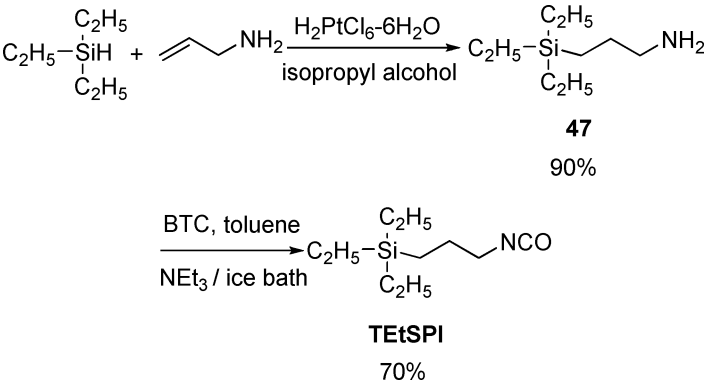
Scheme 20

b. Preparation of Isocyanates

A vast number of bioactive natural products and pharmaceutical drugs, synthesized via intermediate isocyanates, have become very important in the area of polymer products and pharmaceutical chemistry.[56–67]

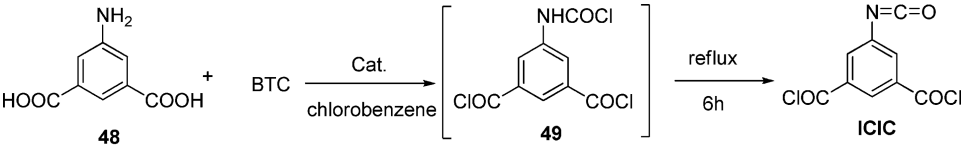
In the field of supermolecular chemistry, most attention has been focused on the synthesis of polymers and block copolymers with controlled molecular weights and well-defined structures. Ahn and co-workers[56] were the first to synthesize the 3-(triethylsilyl) propyl isocyanate (TEtSPI) with the objective to study the effect of a bulky substituent present in an isocyanate monomer in controlling the structure of polyisocyanates *via* living anionic polymerization. TEtSPI was synthesized in a two-step sequence (*Scheme 21*) by hydrosilylation of allylamine with triethylsilane then treatment of the resulting amine with BTC in toluene.

Subsequently, in Zhou's work, the intermediate L-lysine methyl ester diisocyanate (LDI) of amphiphilic block copolymers was synthesized *via* an improved reaction procedure, where L-lysine methyl ester dihydrochloride reacted directly with BTC using CH_2Cl_2 as the solvent and pyridine as the catalyst in the yield of 56%.[57]



Scheme 21

Additionally, a novel reverse osmosis membrane ICIC–MPD (membrane-polyamide-urea) was prepared by Liu and colleagues, where the key functional intermediate ICIC was also synthesized by the reaction of BTC with 5-amido-isophthalio acid **48** in the presence of composite catalyst such as Et_3N/imidazole or pyridine/imidazole (*Scheme 22*).[58]



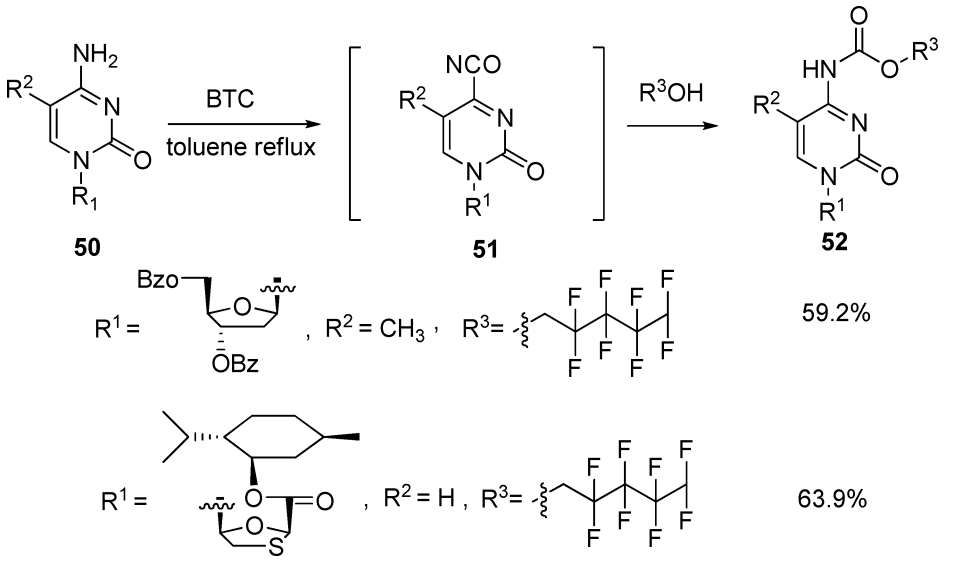
Scheme 22

In other recent studies, functionalized isocyanates have been also used as versatile intermediates in the medicinal chemistry of nucleosides,[62] lipids,[63] and some inhibitors of bioactive natural products such as an inhibitor of fatty acid amide hydrolase[66] and so on.[59–61]

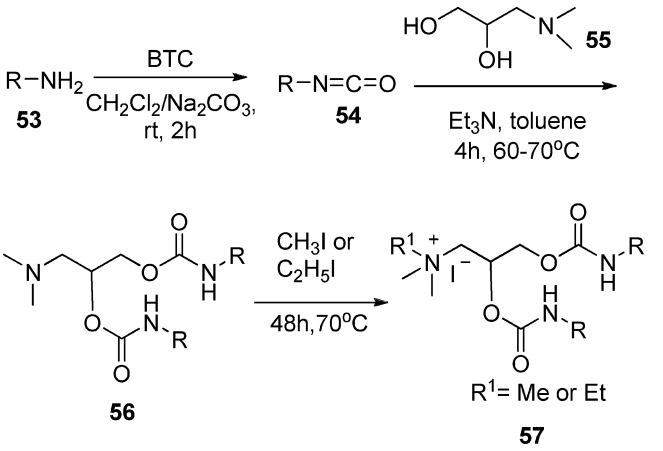
Recently, the method of using an alkyloxycarbonyl group to mask the 4-amino group of cytosine nucleosides has proven to be an important tactic in the design of nucleoside prodrugs. Chen *et al*.[62] investigated N^4-alkyloxycarbonyl cytosine nucleosides as a model and reported the convenient procedure of reacting nucleosides **50** with BTC in refluxing toluene without a base to obtain cytosine nucleosides isocyanates **51**. Subsequent addition of the corresponding alcohols gave the target compounds **52** successfully (*Scheme 23*).

Intermediate alkyl isocyanates **54** were also prepared by the condensation of BTC in CH_2Cl_2 solution with an alkylamine **53** in the presence of Na_2CO_3 solution. The corresponding carbamate-linked lipids **56** and **57** showed good properties as carriers to deliver genes into cells (*Scheme 24*).[63]

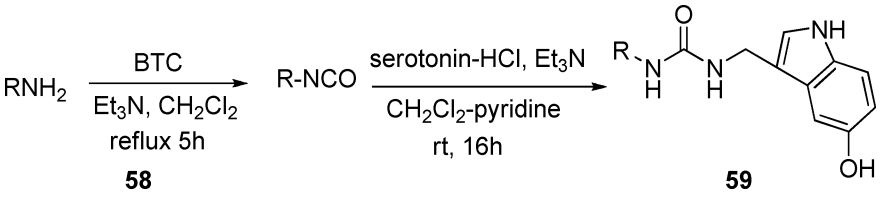
N-Arachidonoylserotonin (AA-5-HT) is an inhibitor of fatty acid amide hydrolase (FAAH).[64] In order to evaluate the potential mechanism of action against pain, a series of analogues was synthesized by Ortar's group. Analogues **59** were synthesized by treatment of the appropriate primary amines **58** with BTC, followed by coupling of the resulting isocyanates with serotonin (*Scheme 25*). The products **59** were generally inactive FAAH inhibitors.[65]



Scheme 23

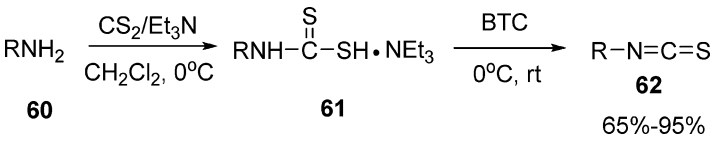


Scheme 24



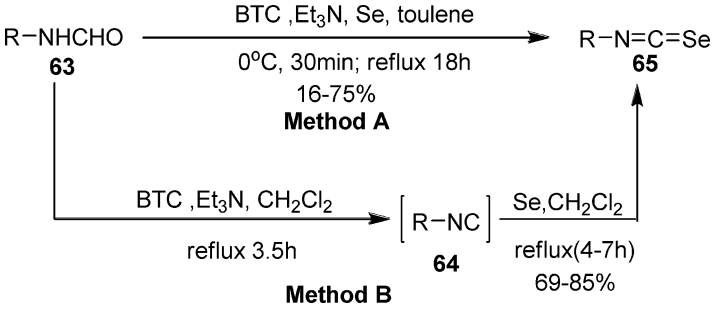
Scheme 25

Isothiocyanates **62** are one of the most important synthetic intermediates for the preparation of both sulfur and nitrogen containing organic compounds, especially heterocycles (*Scheme 26*).[66]



Scheme 26

Fernandez-Bolanos *et al.*[67] developed a new and practical procedure for the preparation of unprotected glycopyranosyl selenoureas and their mild transformation into bicyclic isoureas. Intermediate alkyl and aryl isoselenocyanates **65** were obtained from the corresponding formamides with an excess of BTC, black selenium and Et_3N *via* method A and method B (*Scheme 27*). Method A gave isoselenocyanates **65** in 16–75% yields, however, the yields were improved considerably (69–85%) when used refluxing CH_2Cl_2 instead of toluene in method B.



Scheme 27

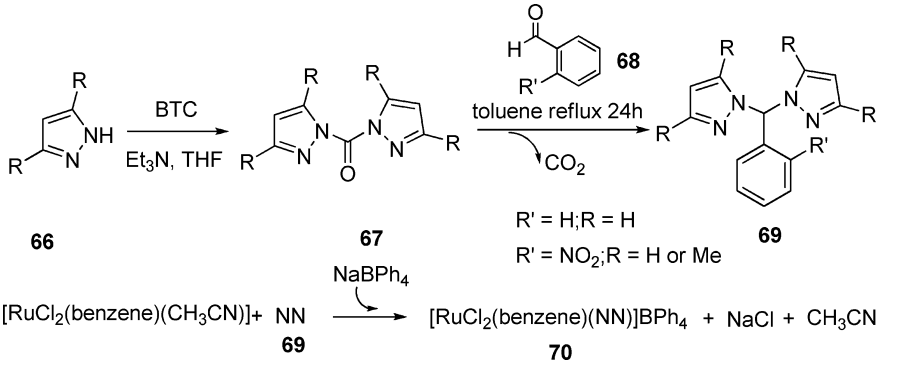
c. Preparation of Ureas

The urea functionality is a structural feature present in many biologically active compounds, such as anti-mycobacterial and anti-trypanosomal agents, plant and insect growth regulators, and as antagonists of natural receptors.[68–71] Ureas can be efficiently synthesized in excellent yields *via* a reaction of excess amines with BTC under the proper conditions.

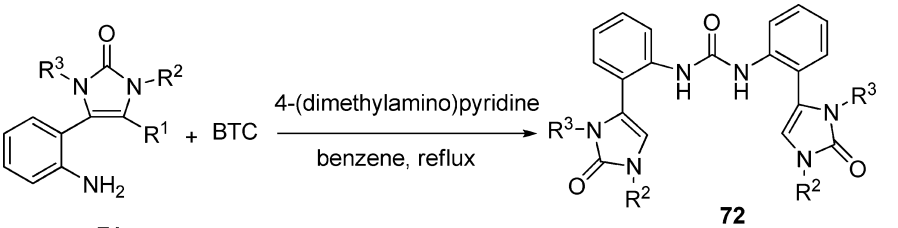
The *bis*-(pyrazol-1-yl)ketones **67** were obtained through the treatment of the pyrazoles **66** with BTC in the presence of Et_3N. In the work of Manzano's group, it was used to synthesize one of the significant intermediates of *bis*-(pyrazol-1-yl)methane ligands (NN) **69** then using these type of ligands to synthesize ruthenium derivatives of the type $[RuCl_2(benzene)(NN)]BPh_4$ **70** (*Scheme 28*).[72]

More recently, the symmetrical ureas **72** were obtained in moderate to good yields by a reaction of the corresponding dihydroimidazolones **71** with BTC in the presence of a catalytic quantity of 4-(dimethylamino)pyridine (*Scheme 29*).[73]

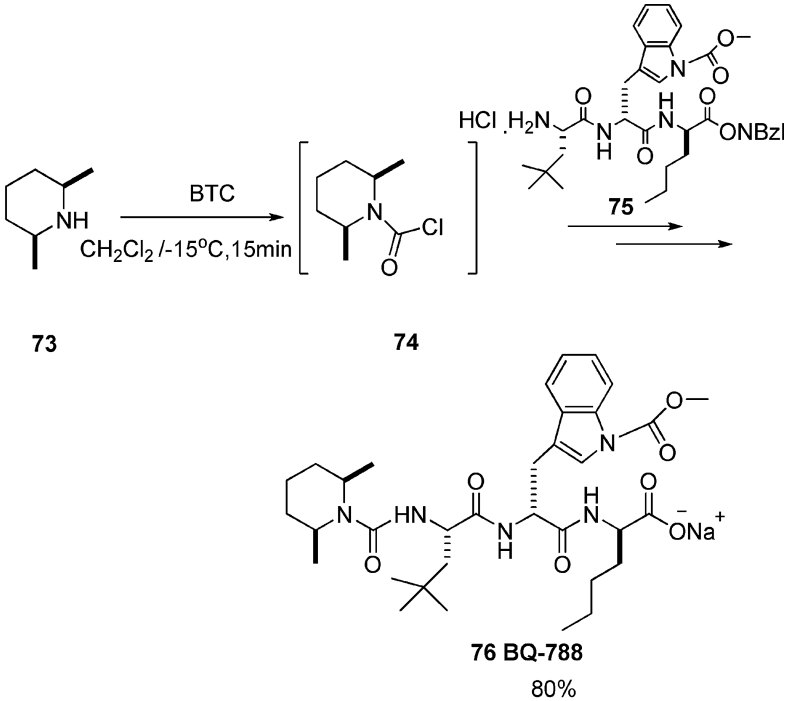
Significant progress has been made in the area of Endothelin-B (ET_B), where BQ-788 was bound to be a very potent and selective ET_B receptor antagonist. The reaction of BTC with amine **73** in CH_2Cl_2 under nitrogen atmosphere proceeded smoothly to provide the reactive intermediate **74**. Coupling with compound **75** formed the highly hindered trisubstituted urea **76 (BQ-788)** (*Scheme 30*).[74]



Scheme 28



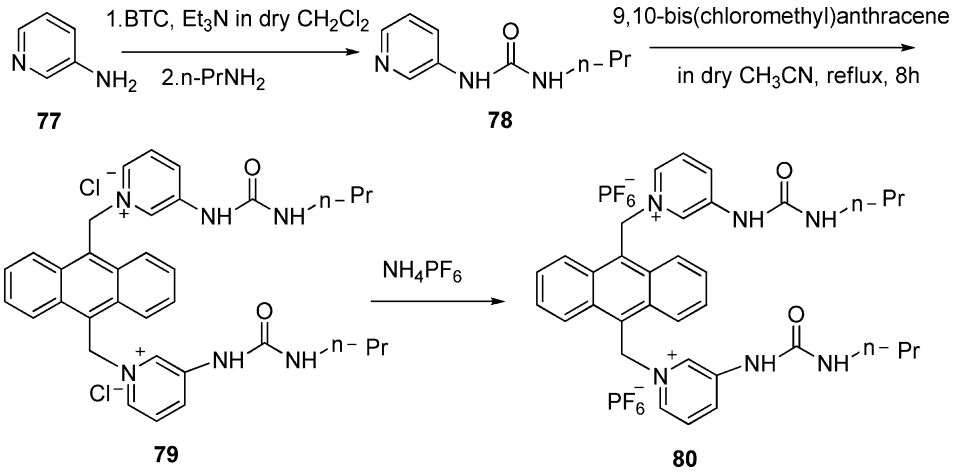
Scheme 29



BQ-788 = *N-cis*-2,6-dimethylpiperidine -1-carbonyl-L-*γ*-methylleucyl-D-1-methoxycarbonyltryptophanyl-D-norleucine sodium salt

Scheme 30

Recently, Ghosh *et al.*[75] reported an anthracene-based ureidopyridyl fluororeceptor for dicarboxylates. Intermediate ureidopyridyl **78** was prepared by reacting 3-aminopyridine with BTC in the presence of Et_3N in dry CH_2Cl_2 followed by slow addition of 1-propylamine. Subsequent coupling of **78** with 9,10-bis(chloromethyl)anthracene followed by anion exchange using NH_4PF_6 afforded the receptor **80** as a light yellow solid (*Scheme 31*).



77 **78** **79** **80**

Scheme 31

Other types of ureas, such as intermediates **82**[82] and **85**,[83] were also accessed by this route[76–81] (*Scheme 32*).

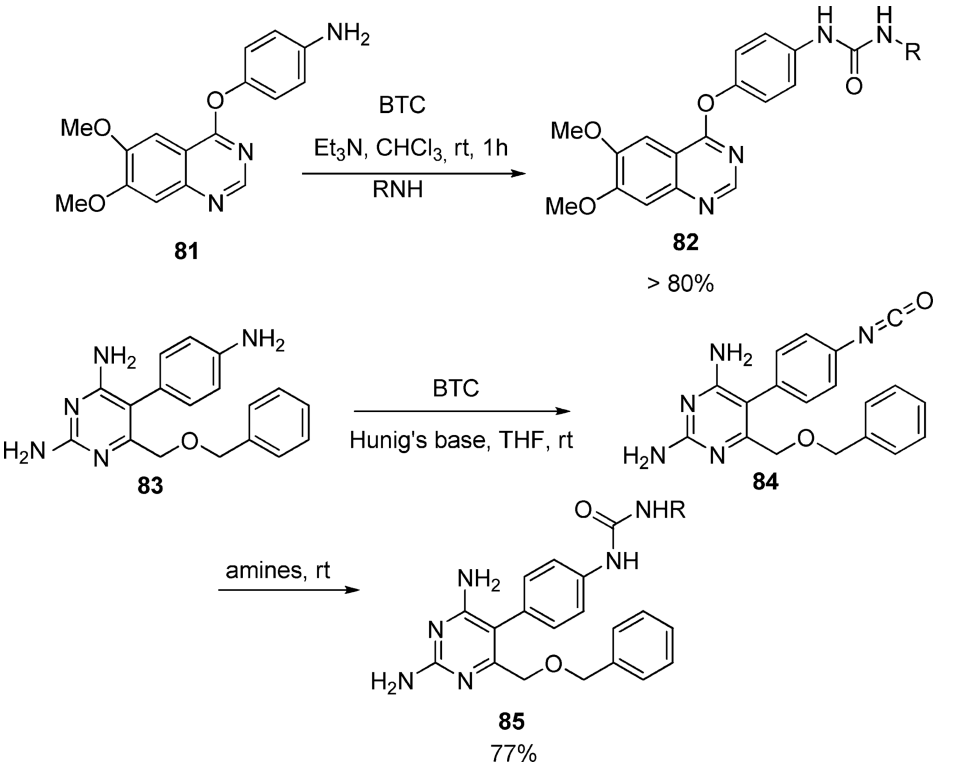
3. Acylation of Aromatic Compounds

In recent years, BTC was used in the acylation of aromatic compounds to obtain the corresponding carbon acylation products.[84] As has been well demonstrated, transition-metal asymmetric catalysis is one of the most powerful tools for the synthesis of optically active compounds,[85] and the development of new chiral ligands represents a crucial part of this area.

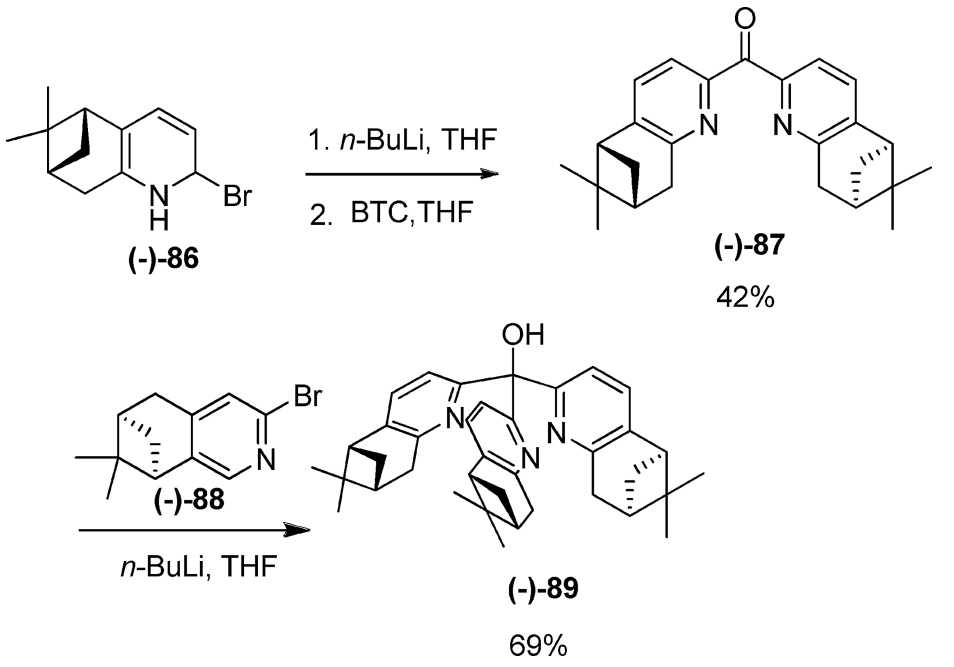
Chiral ligand (−)-**89** is a C_3-symmetric tripodal ligands and the key intermediate ketone (−)-**87** was obtained in a reasonable yield (42%) by the reaction of intermediate (−)-**86** with *n*-BuLi and BTC. Subsequent slow addition of (−)-**88** to afforded ligand (−)-**89** (69%) (*Scheme 33*).[86]

III. Cyclization

Heterocycles form by far the largest of the classical divisions of organic chemistry.[87, 88] Moreover, they are of immense importance both biologically and industrially. Organic chemists have been engaged in extensive efforts to produce heterocyclic compounds by developing new and efficient synthetic transformations. Among the new synthetic transformations, cyclization reactions of compounds containing *N*,*N*-binucleophiles *N*,*O*-binucleophiles or *O*,*O*-binucleophiles with BTC are among the most attractive methodologies for synthesizing a variety of heterocyclic compounds.



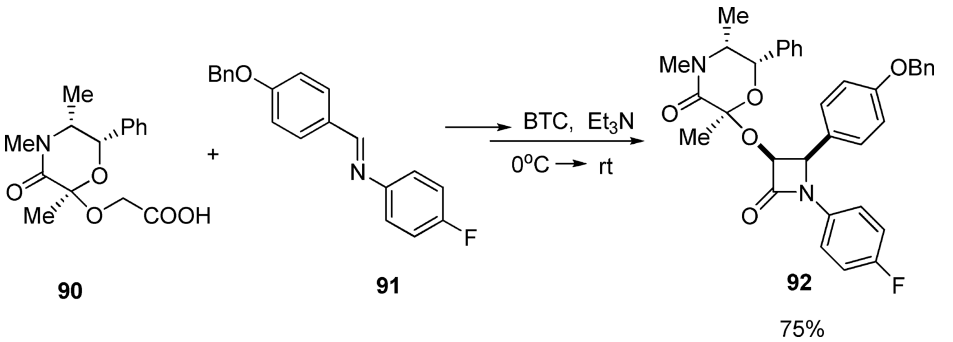
Scheme 32



Scheme 33

1. Synthesis of Four-membered Heterocycles

BTC, known to react with acids to produce acid chlorides or anhydrides, has been successfully employed as an efficient acid activator for the one-step cycloaddition reaction of acids and imines to provide β-lactams. For example, the β-lactam scaffold **92**, which showed potent cholesterol-absorption inhibitory activity, has been synthesized by treatment of BTC with carboxylic acid **90** and imine **91** in presence of Et_3N with up to 75% yield (*Scheme 34*). This method has several advantages including high yield, mild and environmentally friendly reaction conditions, short reaction times and a simple work up procedure.[89]



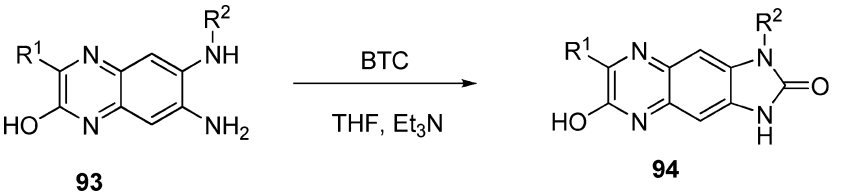
Scheme 34

2. Synthesis of Five-membered Heterocycles

a. Preparation of Imidazolinone Derivatives

Recently, imidazolinone derivatives,[91–93] which appear frequently in drugs and biologically active compounds, have been extensively investigated in both academic and industrial institutions.

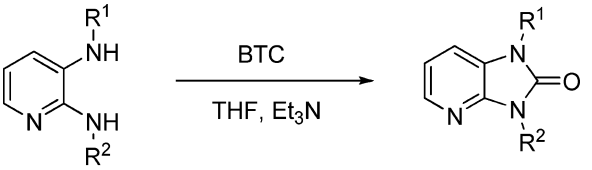
An efficient preparation of various imidazolinone derivatives using BTC from compounds containing either two primary or secondary amino groups has been developed. For example, the 6-hydroxy-1,3-dihydro-imidazo-[4,5-*g*]quinoxalin-2-ones **94** could be easily synthesized under mild conditions by treatment of diamines **93** and BTC in THF for 30 min (*Scheme 35*). The novel compound scaffolds **94**, which integrate two benzofused privileged structures into one molecule, may provide a greater chance for the discovery of novel analogs of *brimonidine*, *iprotiazem*, *droperidol*, *flibanserin*.[94]



R^1= CH_3- R^2 = (3,4-$(CH_3O)_2$)$PhCH_2CH_2$-, $PhCH_2CH_2$-,$CH_3O(CH_2)_3$-
R^1= $(CH_3)_2CHCH_2$- R^2 = $PhCH_2CH_2$-

Scheme 35

Symmetrically and unsymmetrically 1,3-disubstituted-1,3-dihydro-imidazo[4,5-*b*]pyridin-2-ones **96** have been shown to possess antidepressant, antiphlogistic, cardiotonic, hypotensive and antiarrhythmic, and antisecretory activity.[95–99] A general, high-yielding method for the preparation of these novel heterocycles by simple organic synthesis has been demonstrated (*Scheme 36*). The substituted diamines **95** were cyclized into imidazolinone derivatives **96** with up to 97% yield in presence of BTC and Et_3N. The reaction conditions were mild and tolerant of a wide range of functional groups such as phenyl, cyclohexyl, naphthyl, *etc.*[100]



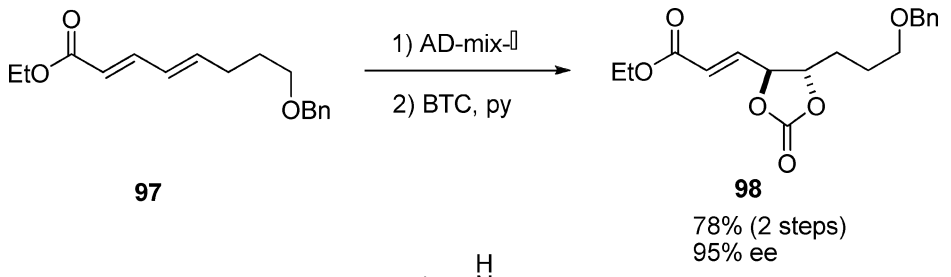
95 **96** (65-97%)

a) $R^1 = R^2 = H$; b) R^1, R^2 = alkyl, aryl

Scheme 36

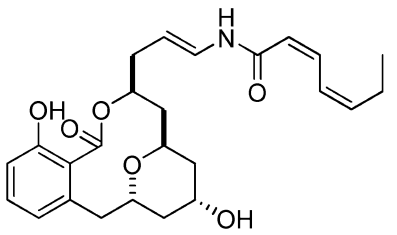
b. Preparation of Cyclic Carbonates

As already shown, BTC is a very useful carbonyl source in organic synthesis. Generally, exposure of a diol to BTC and pyridine bases provided a cyclic carbonate in good to excellent yields.[101–104] For example, dienoate **97** was dihydroxylated under the Sharpless conditions to give a diol, which was cyclized into carbonate **98** in good overall yield (78%) with high enantioselectivity in presence of BTC and pyridine (*Scheme 37*). O'Doherty *et al.*[105] reported that carbonate **98** was the key intermediate in preparation of the natural product (−)-Apicularen which has attracted significant interest due to its extremely potent antitumor activity.



97 **98**

78% (2 steps)
95% ee

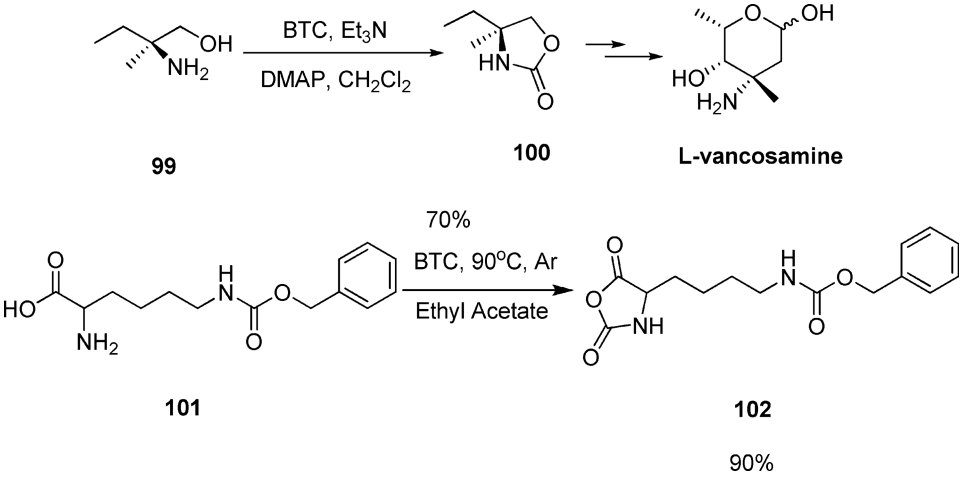


(-)-Apicularen A

Scheme 37

c. Preparation of Oxazolidinone Derivatives

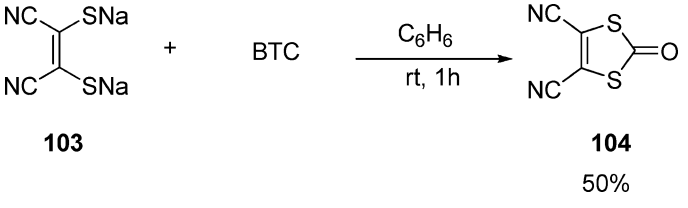
α-Amino acids and α-amino alcohols can react readily with BTC to form some oxazolidinone derivatives.[106–108] For example, (S)-2-amino-2-methylbutan-1-ol **99** could be carbonylated to (S)-4-ethyl-4-methyloxazolidin-2-one **100** by using of BTC in presence of Et_3N and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 with a 70% yield.[109] Compound **100** is an important intermediate to prepare L-vancosamine which is a carbohydrate component of the glycopeptide antibiotics *vancomycin* and *sopraviridin*. Additionally, *N*-ε-Z-lysine **101** treated with BTC in ethyl acetate at 90°C under argon protection provided *N*-ε-benzyloxycarbonyl-L-lysine *N*-carboxyanhydride **102** which can be converted into water-soluble, degradable polymers such as poly(ε-caprolactone)-*g*-poly(L-lysine) (PCL-*g*-PLL) by an anionic ring opening polymerization reaction (*Scheme 38*).[110]



Scheme 38

d. Preparation of Other Five-membered Heterocycles

Treatment of BTC instead of gaseous phosgene[111] with disodium dimercaptomaleonitrile **103** can produce 4, 5-dicyano-1,3-dithiol-2-one **104**, which has been utilized as a useful synthetic precursor for the preparation of various organic compounds (*Scheme 39*).



Scheme 39

4,5-Dicyano-1,3-dithiol-2-one 104. Typical Procedure.[111] *A solution of BTC (3.75 g, 0.013 mol) in benzene (35 ml) was added to a suspension disodium dimercaptomaleonitrile* ***103*** *(7.05 g, 0.04 mol) in benzene (70 ml) in a period of 15 min under ice cooling. The*

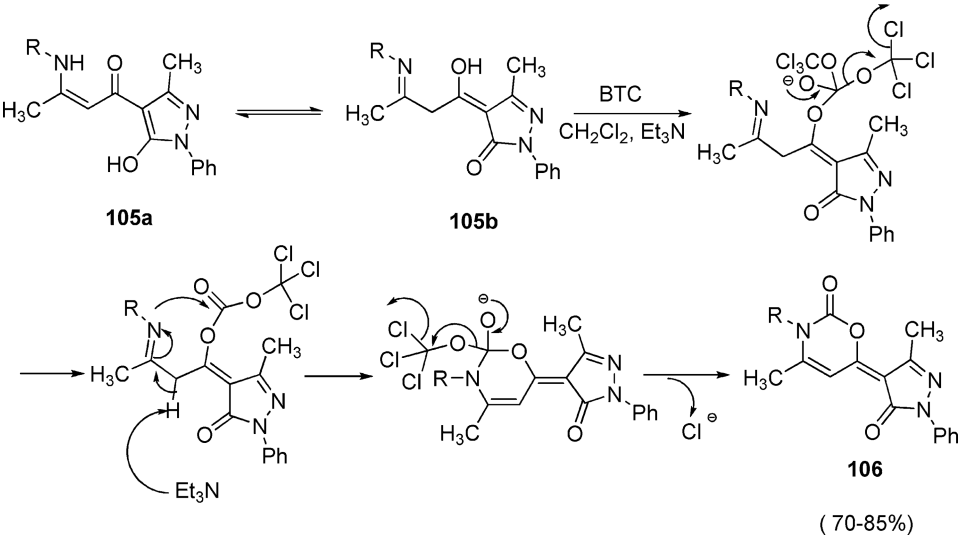
mixture was stirred for 1 h at room temperature, filtered, and evaporated. The crude product was purified by chromatography on a silica gel column with petroleum ether-ethyl acetate (10:1) as eluent. The second fraction was collected and recrystallized from carbon tetrachloride to give 4,5-dicyano-1,3-dithiol-2-one ***104*** *as colorless needles, yield: 1.57 g (50%), mp 121–123°C.*

3. Synthesis of Six-membered Heterocycles

a. Preparation of Oxazinone Derivatives

1,3-Oxazines belong to a class of compounds that have been largely studied due to their wide range of biological activities and easy synthetic accessibility.[112–117]

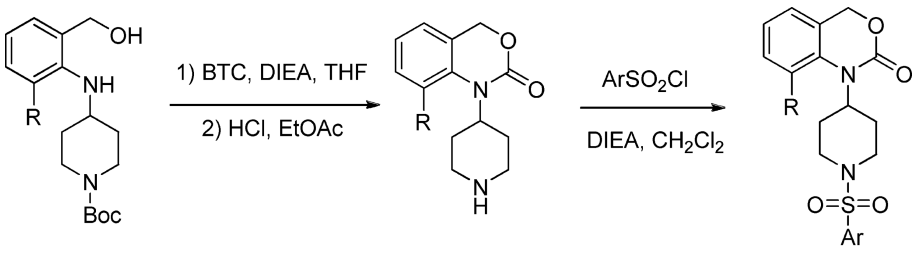
The target compounds, *N*-substituted pyrazolo-1,3-oxazin-2-ones **106**, were obtained by the ring closure of pyrazolo-β-enaminones **105** with BTC in dichloromethane in the presence of triethylamine. A possible mechanism is shown in *Scheme 40*.[7]



Scheme 40

N-Substituted Pyrazolo-1,3-oxazin-2-ones 106. Typical Procedure.[7] *To a cooled (0°C) solution of the appropriate enaminone* ***105*** *(5 mmol) and triethylamine (10 mmol) in 40 ml of dichloromethane, triphosgene (1.66 mmol) was slowly added dropwise under magnetic stirring. After being gradually warmed to room temperature, the resulting mixture was stirred for 48 h. Water was added, followed by extraction with dichloromethane. The organic layer was dried over sodium sulfate and evaporated to dryness to give the desired compounds* ***106*** *as a white solid.*

Recently, a new series of selective 5-HT_6 ligands (benzoxazinepiperidinyl sulfonamides **109**) have been studied for their antibacterial and antibiotic activities. These sulfonamides could be synthesized *via* the key intermediate 1-piperidin-4-yl-1,4-dihydrobenzo[*d*][1,3]oxazin-2-ones **108**, which was derived from compounds **107** and BTC in presence of *N*,*N*-diisopropylethylamine (DIEA) in THF (*Scheme 41*).[118]



107 **108** **109**

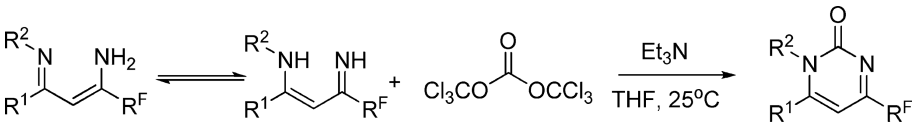
R = H, Me

Scheme 41

b. Preparation of Pyrimidinone Derivatives

Over the past decade, the synthesis of pyrimidinone derivatives have attracted the attention of many researchers because of their wide range of biological activities such as anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive activities.[119–122]

Fustero *et al.*[123] reported that a series of versatile fluorinated 1, 3-vinylogous amidines **110**, react with BTC to form new fluorinated pyrimidin-2(1*H*)-ones **111** in high yields. These analogs are currently being investigated as insecticides, herbicides, and pharmaceuticals.



110 **111**

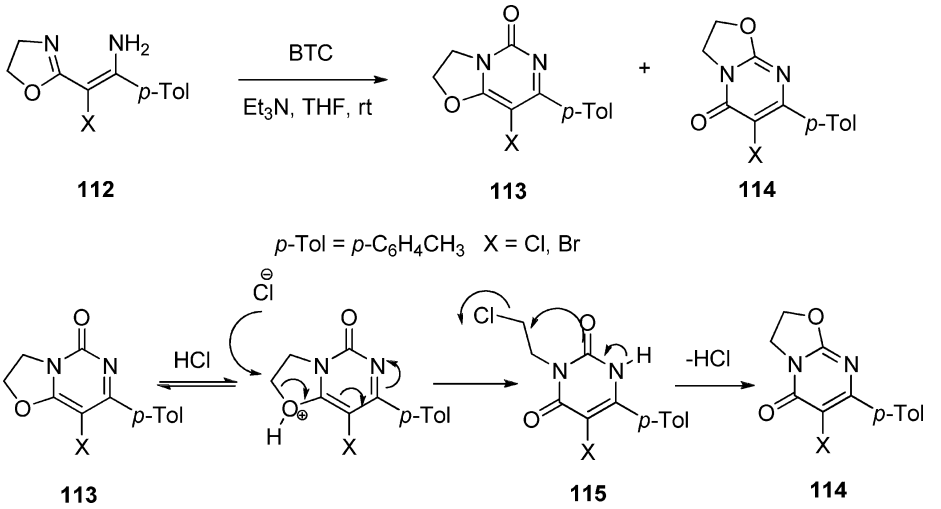
(70-94%)

R^1 = alkyl, aryl; R^2 = alkyl, aryl; R^F = $CF_2C_6H_5$, $CF_3(CF_2)_6$, CF_2(β-$C_{10}H_7$)

Scheme 42

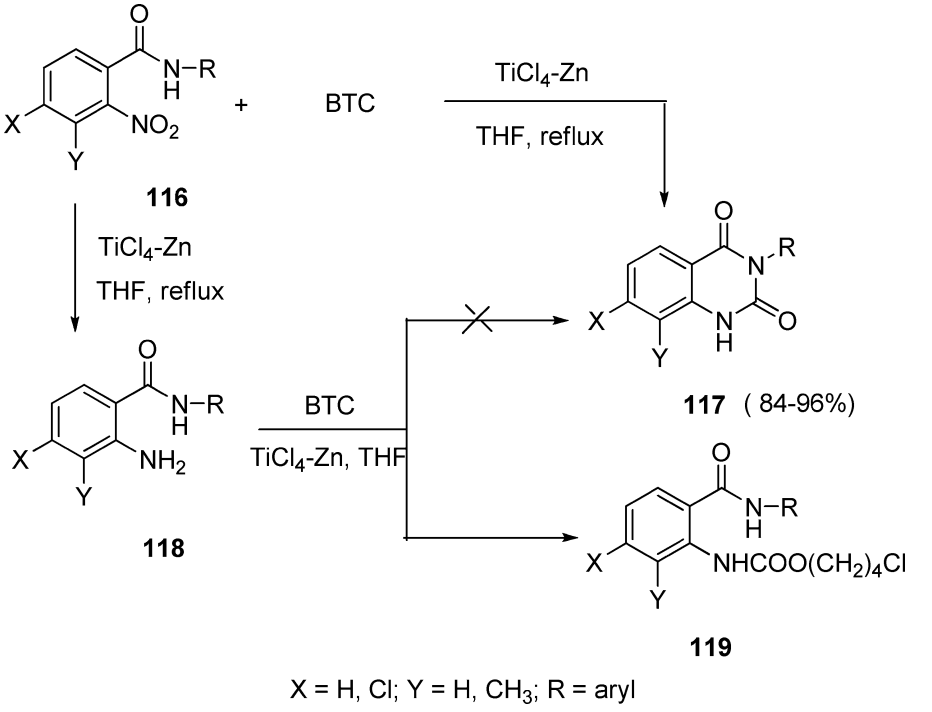
Fluorinated Pyrimidin-2(1H)-ones 111. Typical Procedure.[123] *A solution of BTC (1.0 equiv) in THF was added to a solution of compound* ***110*** *(1.0 equiv) and* Et_3N *(2.0 equiv) in THF at room temperature. The reaction mixture was stirred until the starting material was no longer present (0.5–3 h, TLC analysis). Standard work-up furnished crude derivatives* ***111****, which were then purified by means of flash chromatography to afford fluorinated pyrimidin-2(1H)-ones* ***111*** *in yields that ranged from 70–94%.*

Condensation of the protected, halogenated β-enamino acids **112** with BTC yielded a mixture of the corresponding isomeric oxazolopyrimidinones **113** and **114**, respectively. Compounds **114** might arise from uracils **113** *via* intermediates **115**. Thus, chloride anion generated in the reaction of **112** with BTC might cause a nucleophilic ring-opening reaction to give intermediates **115**, which might undergo an alternative ring-closing reaction in the presence of Et_3N to generate the isomeric uracils **114** (*Scheme 43*).[124]



Scheme 43

Recently, Shi's group demonstrated an efficient one-pot method for preparation of quinazoline-2,4-diones **117** from 2-nitrobenzamides **116** and BTC, using $TiCl_4$/Zn system as reducing reagent in THF at reflux (Scheme 44).[125]

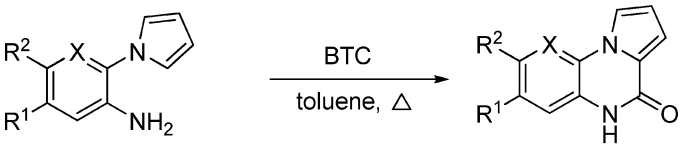


Scheme 44

Usually, nitro compounds are easily reduced to amines by a low-valent titanium reagent, thus the intermediate amine **118** was considered to be formed first and then reacted with BTC to give product **117**. However, when 2-nitrobenzamides **116** was first reduced to 2-aminobenzamides **118** by the low-valent titanium reagent, and then reacted with BTC under the same conditions, carbamates **119** were surprisingly obtained as final products (*Scheme 44*). No quinazoline-diones **117** were observed. This indicated that the nitro compound was not simply reduced to intermediate amines in this reaction.

c. Preparation of Other Six-membered Heterocycles

A simple, high-yielding method for preparation of quinoxalinone derivatives which are of biomedical and pharmaceutical interesting has been developed. For example, cyclization (*Scheme 45*) was possible between the NH_2 of **120** and the C-α of the pyrrole ring by reacting with BTC in toluene to give the quinoxalinones **121** which were, in this case important intermediates in the preparation of antimalarial drugs.[3]



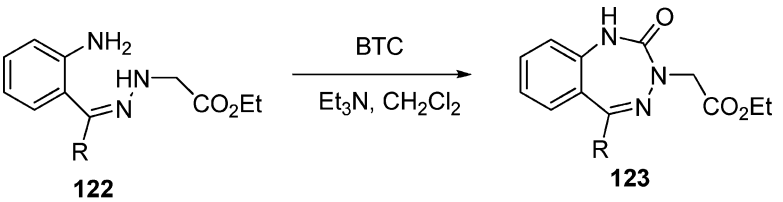
120 **121**

R^1 = H, OCH_3 ; R^2 = H, OCH_3, Cl ; X = C, N (53 - 90%)

Scheme 45

4. Synthesis of Multi-membered Heterocycles

Treatment of BTC with diamine **122** in the presence of Et_3N in CH_2Cl_2 could provide the seven membered-ring 1,3,4-benzotriazepine derivatives **123** in up to 100% yield (*Scheme 46*). Recently, reports have shown that analogues of compounds **123** display high selectivity for CCK_1 receptors and potent in vivo inhibition of gastrin-mediated gastric acid secretion.[4, 5]



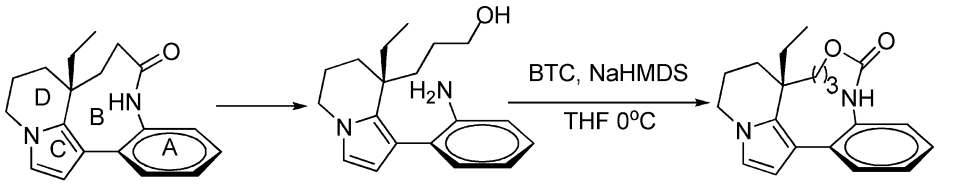
122 **123**

R = 2-Py, Ph, *c*-C_6H_{11}

Scheme 46

Macrocyclic analogues of (−)-rhazinilam **124**, having an 11-membered B-ring with an endocyclic carbamate group, were synthesized from the natural product. The series of compounds **125** were obtained by opening of the lactam ring of (−)-rhazinilam **124**,

reduction of the carboxylic acid to the corresponding primary alcohol and ring reclosure. However, these analogues of rhazinilam with a larger B-ring containing an additional C–O bond, displayed a very weak activity on inhibition of microtubule assembly and disassembly (*Scheme 47*).[126]



124 **125**

21%

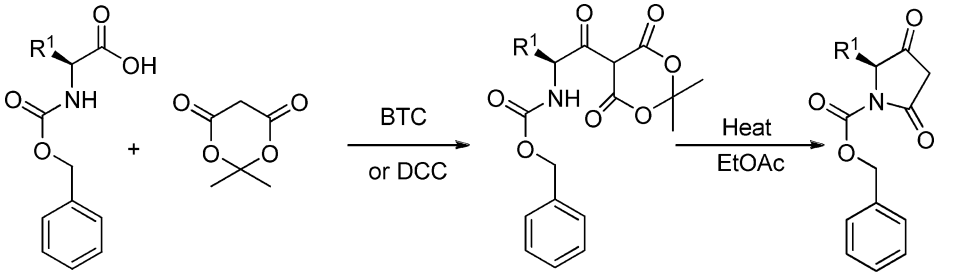
NaHMDS = sodium *bis*(trimethylsilyl)amide

Scheme 47

IV. Dehydration Reactions

1. Preparation of Lactams

BTC has also proved to be one of the most useful dehydration agents.[127] Lactams, such as *N*-benzyloxycarbonyl lactams **127** could be obtained from *N*-benzyloxycarbonyl acids **126** by reaction with 2,2-dimethyl-1,3-dioxane-4,6-dione and BTC as the dehydration agent, as well as DCC, followed by heating in EtOAC in a one-pot reaction (*Scheme 48*).[128]

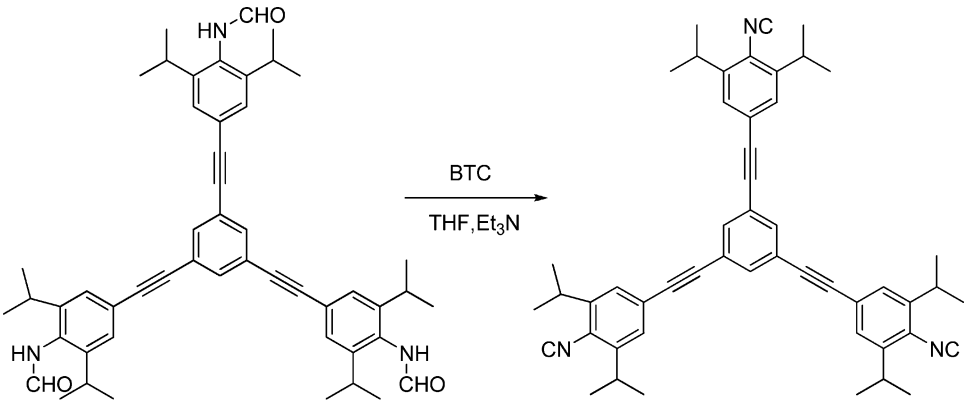


126 **127**

Scheme 48

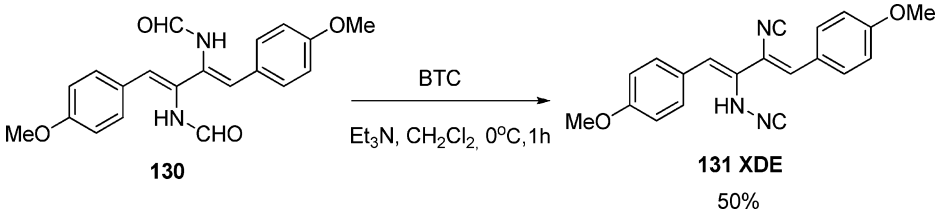
2. Preparation of Isocyanides

Paek *et al.* recently prepared various transition-metal complexes of organic isocyanides containing the triisocyanide ligand 1,3,5-tris[(4-isocyano-3,5-diisopropylphenyl) ethynyl]benzene **129**, which exhibited interesting photophysical properties. The triisocyanide ligand **129** was prepared smoothly in high yield by the dehydration reaction of **128** with BTC in the present of Et_3N.[129, 130]



Scheme 49

A similar process was reported by another group,[131] where the xanthocillin derivative **131**, which showed thrombopoietin receptor agonist activity, was synthesized through the dehydration reaction of intermediate **130** with **BTC**/Et_3N in good yield (*Scheme 50*).

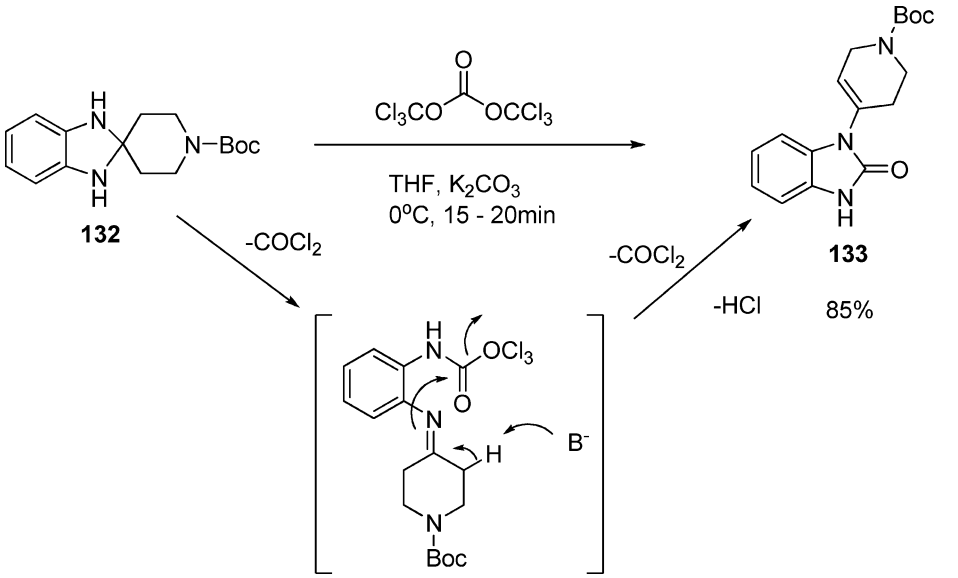


Scheme 50

V. Rearrangement Reactions

As far as we know, rearrangement reactions using BTC as an auxiliary reagent have rarely been described. However, Jeffrey *et al.*[6] recently reported that *N*-alkenyl-benzimidazol-2-one **133** can be readily prepared from spiro-benzimidazoline **132** using BTC and potassium carbonate as primary reagents. This rearrangement reaction was complete almost instantaneously and the only detectable reaction by-products were *o*-phenylenediamine and the corresponding ketone piperidin-4-one. These by-products were easily removed by chromatography. A plausible rearrangement mechanism is shown in *Scheme 51*.

N-Alkenylbenzimidazol-2-ones (133). Typical Procedure.[6] *To a stirred solution of 1.00 mmol of compound* ***132*** *in 10 mL of THF was added 691 mg (5.00 mmol) of powdered K_2CO_3. The resulting slurry was cooled to 0°C and 119.0 mg (0.40 mmol) of BTC in 2 mL of THF was added dropwise. The mixture was stirred for 15–30 min and quenched with 15 mL of water. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography.*



Scheme 51

VI. Vilsmeier Reaction

A wide variety of reactions using the Vilsmeier reagent have been developed since its discovery in 1927,[133] and they have been applied to the synthesis of a number of organic compounds.[134] Initially, the Vilsmeier reaction was used as a powerful synthetic tool for the formylation of activated aromatic substrates and heteroaromatic compounds.[135, 136] Subsequently, it developed to be one of the most common methods of annulating to aromatic compounds or heterocycles.[137, 138] In addition, certain striking applications such halogenation, haloalkylation, and ring-opening reactions have been more recently investigated.[139–143] Recently, the application of the Vilsmeier reagent in solid state reactions has attracted widespread attention.[144–146]

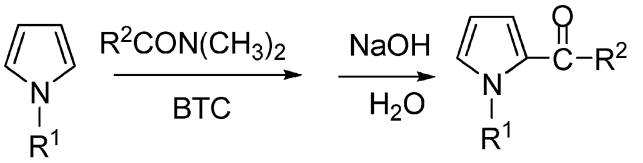
The traditional Vilsmeier reagent involves a combination of dialkyl formamides such as DMF with an acid halide, frequently phosphorus oxychloride ($POCl_3$).[147–149] Recently, BTC and DMF have been used to prepare the Vilsmeier reagent (halomethyleniminium salt) in order to avoid the formation of phosphorous salts[150] and to provide mild reaction conditions.

Current work in our labs is focused on the wide-ranging reactivity of this Vilsmeier reagent (BTC/DMF) to extend its utility by reaction with an extensive set of substrates.

1. Acylation

The acetylation of various electron-rich aromatic and heteroaromatic substrates using the traditional Vilsmeier reagent has been explored.[151–152] 2-Acylpyrrole derivatives are a family of compounds which have many pharmacological activities such as antipyretic, analgesic, and anti-inflammation.[153] In order to find a method which is suitable for industrial applications from the standpoint of safety and environmental acceptability, our group[154] designed and carried out the introduction of carbonyl group into pyrrole derivatives using

Vilsmeier reagent derived from BTC/N,N-dimethylacylamide (*Scheme 52*). It was noticed that the reaction temperature was very important as treatment of heteroaromatic compounds with the Vilsmeier reagent (1.0 equiv) above 60°C generated a black and viscous reaction mixture.



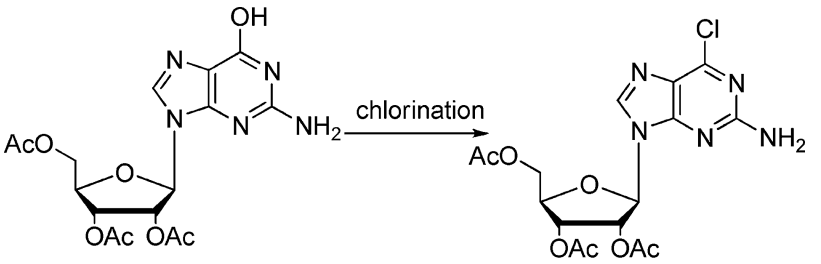
(84-92%)

a) R^1 = H, R^2 =CH_3; b) R^1 =H, R^2 = CH_2CH_3; c) R^1 = H, R^2 = C_6H_5; d) R^1 =H, R^2 =*p*-$CH_3C_6H_4$; e) R^1 =CH_3, R^2 =CH_3; f) R^1 =CH_3, R^2 = CH_2CH_3; g) R^1 = CH_3, R^2 = C_6H_5; h) R^1 =CH_3, R^2 = *p*-$(CH_3)C_6H_4$

Scheme 52

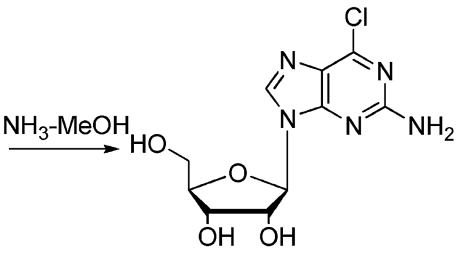
2. Chlorination

The reaction for the chlorination of hydroxy groups is shown in *Scheme 53*.[155] 2′,3′,4′-tri-*O*-acetylguanosine **134** first reacted with the BTC/DMF complex to yield product **135**,



134

135
81%



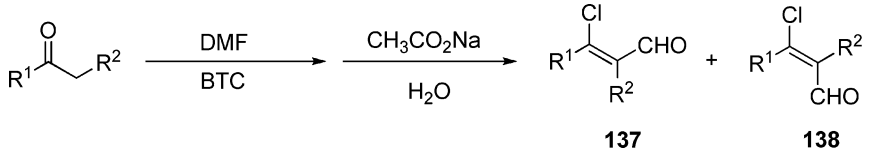
136

Scheme 53

followed by addition to NH_3-MeOH to afford the corresponding 2-amino-6-chloro-9-β-D-ribofuranosylpurine **136**. *N,N*-dimethylaniline which influenced the quality of product was discarded in the chlorination reaction of 6-hydroxy group in guanosine. The phosphoryl chloride which accelerated bond rupture in guanosine was replaced by BTC. The technological improvement of chlorination reaction has several advantages such as high yield, environmentally friendly, simple work up procedure and less side-reaction.

3. Chloroformylation

Many methyl ketones, as well as acyclic methylene ketones and aryl methylene ketones, are converted by the Vilsmeier reagent (BTC/DMF) into β-chlorovinylaldehydes (*Scheme 54*).[156] β-Chlorovinylaldehydes are important starting materials for many natural products,[157] pharmaceutical,[158] and pesticide compounds.[159] Generally, aryl ketones gave better yields than alicyclic ones in this chloroformylation reaction. The monochloroformylation usually produced a mixture of the (*Z*)-isomer **137** and the (*E*)-isomer **138**. The study has shown the influence of the substituent group R^2 on the (*Z*/*E*) ratio of products: *p*-substituted and unsubstituted acetophenones gave (*Z*)-isomers **137** exclusively, but in the case of phenyl ethyl ketone ($R^1 = C_6H_5$, $R^2 = CH_3$) the major product was the (*E*)-isomer **138**.



137 **138**

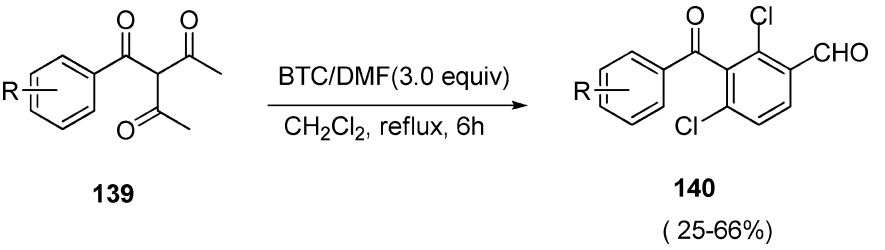
a) $R^1 = C_6H_5$, R^2 = H; b) R^1 = *p*-$(CH_3)C_6H_4$, R^2 = H; c) R^1 = *p*-$(CH_3O)C_6H_4$, R^2 = H; d) R^1 =*p*-ClC_6H_4, R^2 = H; e) R^1 = *p*-BrC_6H_4, R^2 = H; f) R^1 = 4-(CH_3)-3-$(NO_2)C_6H_3$, R^2 = H; g) $R^1 = C_6H_5$, $R^2 = CH_3$; h) R^1 = *p*-$(CH_3)C_6H_4$, $R^2 = C_6H_5$; i) R^1-R^2 = 1, 2-$C_6H_4(CH_2)_2$; j) R^1-$R^2 = (CH_2)_3$; k) R^1-$R^2 = (CH_2)_4$

Scheme 54

4. Aromatization

Some aliphatic substances such as acyclic ketones,[160] cyclohexenones,[161] α, β-epoxy ketones[162] and other compounds[163–167] could be annulated to aromatic compounds through reaction with the Vilsmeier reagent. The postulated mechanism has indicated that the formation of the aromatic ring is quite complex and also results in the generation of some products such as halogenated aromatic aldehyde, halogenated aromatic dialdehyde and halogenated aromatic trialdehyde.[168]

The aromatization of substituted 3-benzoylpentane-2,4-diones **139** with BTC/DMF to give substituted 3-benzoyl-2,4-dichlorobenzaldehydes **140** occurred in moderate yields (25–66%) (*Scheme 55*).[169] It was found that the yields were affected strongly by different substituents on the aromatic ring. The substrates with strong electron-donating groups provided higher yields than those with electron-withdrawing groups.



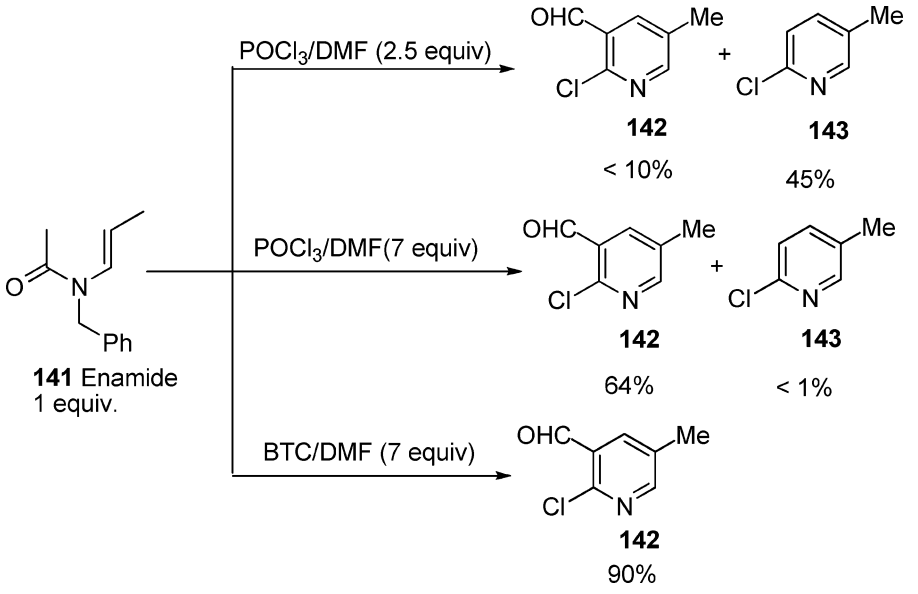
139 **140** (25-66%)

Scheme 55

5. Cyclization

Presently, Vilsmeier cyclization is being developed to be a powerful synthetic tool for the construction of the heterocyclic compounds.[170–175] Theoretically, the cyclization reaction employing amidic carbonyl compounds[176] and carboxylic acids[177, 178] as starting materials leads to multiple iminoalkylations in the presence of excess reagent and the resulting intermediates undergo cyclization to afford heterocyclic compounds under controlled conditions.

Chloronicotinaldehydes are very good precursors for the synthesis of heterocyclic analogues of the arachidonic acid metabolite 8-HETE.[179, 180] The chloronicotinaldehyde **142** was prepared in high yields (88–94%) by the cyclization of enamide **141** when treated with 7.0 equiv BTC/DMF (*Scheme 56*).[181] Upon using 2.5 equiv of Vilsmeier reagent,

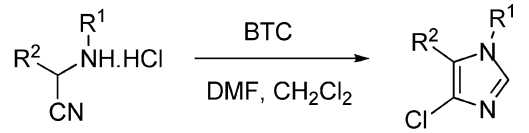


Scheme 56

the yield of chloronicotinaldehyde **142** was less and 2-chloro-5-methylpyridine **143** was the major product. The reactions have shown that the selectivity toward the formation of **142** improved upon increasing ratio of enamide **141/**Vilsmeier reagent. The postulated mechanism suggests that excess Vilsmeier reagent (7 equiv) could trigger the diformylation

of enamides **141** followed by cyclization to afford chloronicotinaldehyde **142** selectively. Compared with the classical method of using $POCl_3$ in the formation of Vilsmeier reagent, the protocol employing the BTC/DMF as Vilsmeier reagent provided the same selectivity in higher yields.

As is well documented, imidazole is the basic mother nucleus of various drugs such as *etomidate*, *cimetidine*, *omeprazole*, and *lansoprazole*.[182] In order to develop a general method for the synthesis of various imidazole derivatives, Borggraeve *et al*.[183] undertook the preparation of imidazole derivatives starting from α-aminonitriles using the BTC/DMF complex. Although the Vilsmeier reagent is an effective acylating reagent for formylation of activated aromatic rings,[184] this formylation did not seem to compete with imidazole formation in this reaction and the product 5-disubstituted-4-chloroimidazoles were obtained exclusively. Only if the reaction time was prolonged (36 h), mere traces of formylated products of **146** and **147** detected by mass spectroscopy (*Scheme 57*).

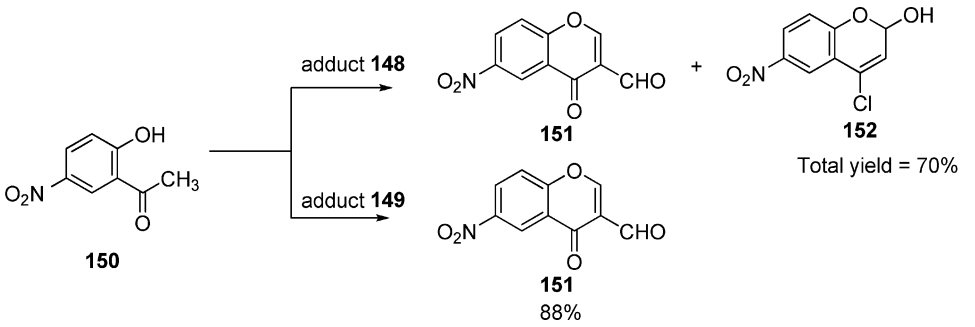


144 $R^1 = Ph_2CH$, $R^2 = H$
145 $R^1 = PMB$, $R^2 = Me$

146 56%
147 62%

Scheme 57

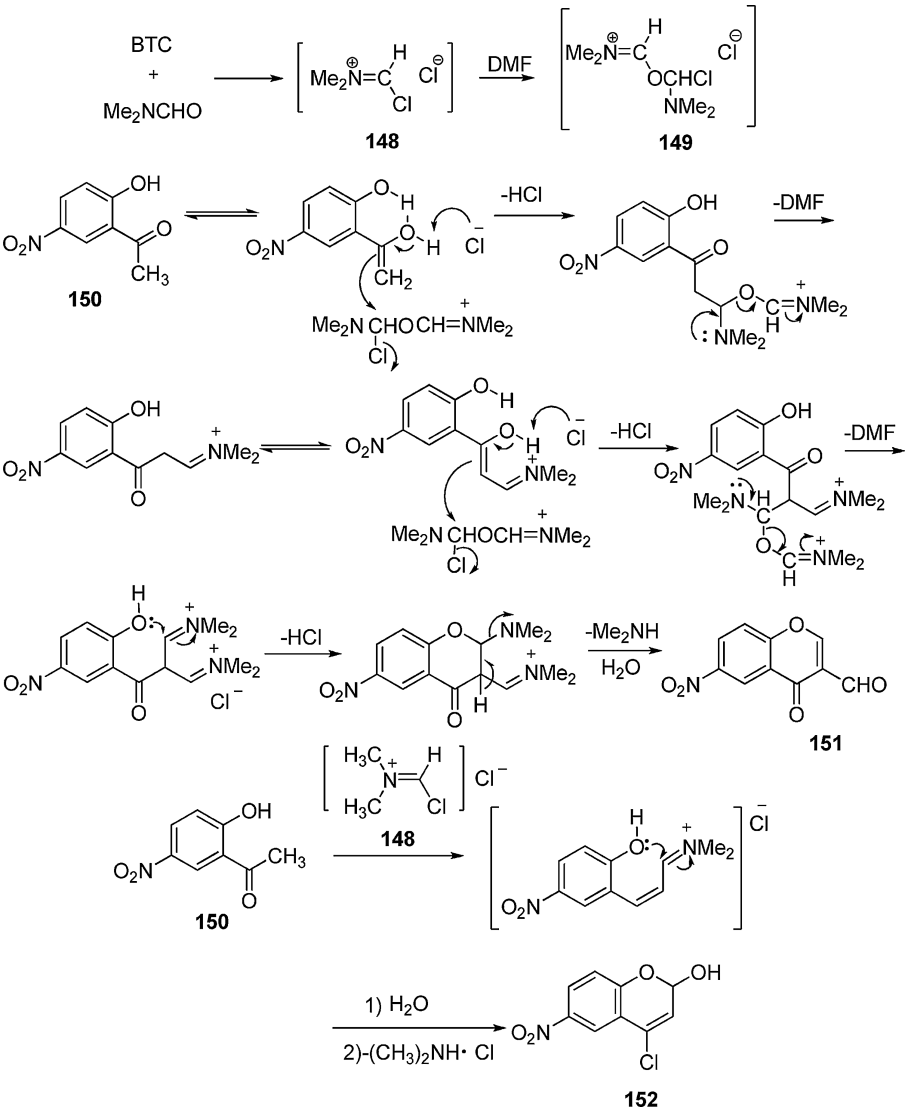
Cyclization of O-hydroxyacetophenones by the Vilsmeier reagent (BTC/DMF) to 3-formylchromones derivatives has been surveyed (*Scheme 58*).[185] This study has demonstrated that if the ratio of 150/BTC/DMF = 1:2:8 was used, the desired chromone 151 was obtained accompanied by the unexpected by-product **152** in 70% total yield (**151**/**152** = 7:3).



Scheme 58

Rivero *et al.*[10] pointed out that the Vilsmeier-type reagent **149** generated *in situ* from BTC and excess DMF, was less reactive than adduct **148** (*Scheme 59*). So when a larger excess DMF was used (**150**/BTC/DMF = 1:2:12), 5-nitro-2-hydroxyacetophenone reacted with the less active adduct **149** and afforded the product **151** exclusively. The results have showed that 1:2:12 ratio of O-hydroxyacetophenones/BTC/DMF was effective for

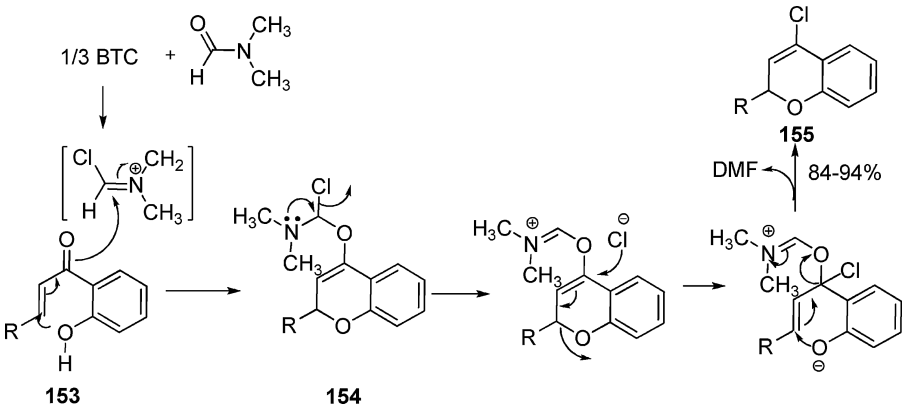
obtaining the good yields of related derivatives (70–95%). A tentative mechanism of the Vilsmeier-Haack reaction of 5-nitro-2-hydroxyacetophenone **150** is depicted in *Scheme 59*.



Scheme 59

Intramolecular cyclization of 2′-hydroxychalcones **153** with BTC/DMF proceeded smoothly to provide 2*H*-4-chlorochromenes **155** in high yields (84–94%).[186] A proposed mechanism proceeds *via* ring closure of **153** to give an enolate, and attack on the enolate oxygen atom to give intermediate **154**. Subsequently, intermediate **154** could yield the corresponding 2*H*-4-chlorochromenes **155** as illustrated in *Scheme 60*.

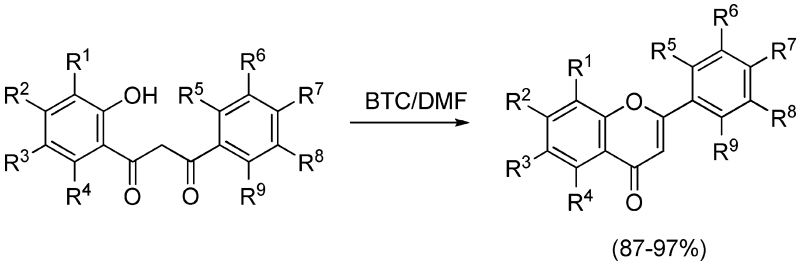
Compound 155. Typical Procedure.[186] *BTC (0.9 g, 3 mmoles) in $ClCH_2CH_2Cl$ (10 ml) was added dropwise to a solution of DMF (0.9 ml, 9 mmoles) in $ClCH_2CH_2Cl$ (5 ml) immersed in an ice-water bath. The mixture was stirred for 20 min to obtain the*



Scheme 60

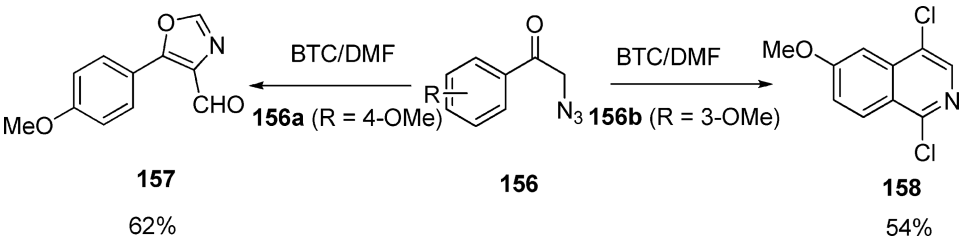
Vilsmeier reagent. Then substituted 2'-hydroxychalcones 153 (3 mmoles) in $ClCH_2CH_2Cl$ (15 ml) was added dropwise to the mixture at 0–5°C. The reaction mixture was stirred at room temperature for 30 minutes and maintained on a oil bath at 80°C for 1–3 h. After completion of the reaction (monitored by TLC [ethyl acetate/cyclohexane = 1:50]), the mixture was poured into ice-water. The organic layer was separated and the aqueous layer extracted with $ClCH_2CH_2Cl$ (10 ml × 2). The combined organic layer washed successively with brine (20 ml × 3) and dried over anhydrous magnesium sulfate. After filtrate and condensation, the residue was separated by column chromatography (silica gel-cyclohexane) to obtain the pure product 155.

There are several methods for the synthesis of flavones by means of cyclization of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones under the conditions of strong acid.[187, 188] Recent research on the construction of flavones using the Vilsmeier reagent (BTC/DMF) has led to the development of a route which affords excellent yields (87–97%) (*Scheme 61*).[189] It is worthwhile noting that electron-withdrawing and electron-donating groups on the aromatic ring do not seem to affect the yield or rate of reaction significantly.



Scheme 61

Our group[190] described a mild and efficient one-step synthesis of substituted 1,4-dichloroisoquinolines and 5-aryloxazole-4-carboxaldehydes from various phenacyl azides under Vilsmeier conditions. The phenacyl azides derivatives **156** afforded either **157** or **158** depending on the location of the methoxy group at the *para* or *meta* positions respectively (*Scheme 62*). The mechanism for formation of **157** and **158** is depicted in *Scheme 63*.



Scheme 62

6. Ring-opening Reactions

A method for the efficient and highly regioselective synthesis of β-haloamines **160** *via* the ring-opening of *N*-tosylcyclohexylaziridine **159** using the Vilsmeier reagent generated *in situ* from BTC and DMF has been elaborated by Singh *et al.* (*Scheme 64*).[191]

The ring cleavage reaction was highly stereoselective as only one product was formed and in excellent yield. Oxalyl chloride, BTC and phosphorous tribromide in combination with DMF as the activating Vilsmeier agents were also tested. The results indicated that formation of β-haloamine **160** using BTC/DMF required the shortest reaction time.

When treated with ionic nucleophiles LiBr and NaCl in DMF at room temperature, *N*-tosylcyclohexylaziridine **159** was not converted to the desired β-haloamine **160**. The results established that the activated BTC/DMF complex facilitates the ring-opening reaction by coordination with the aziridine.

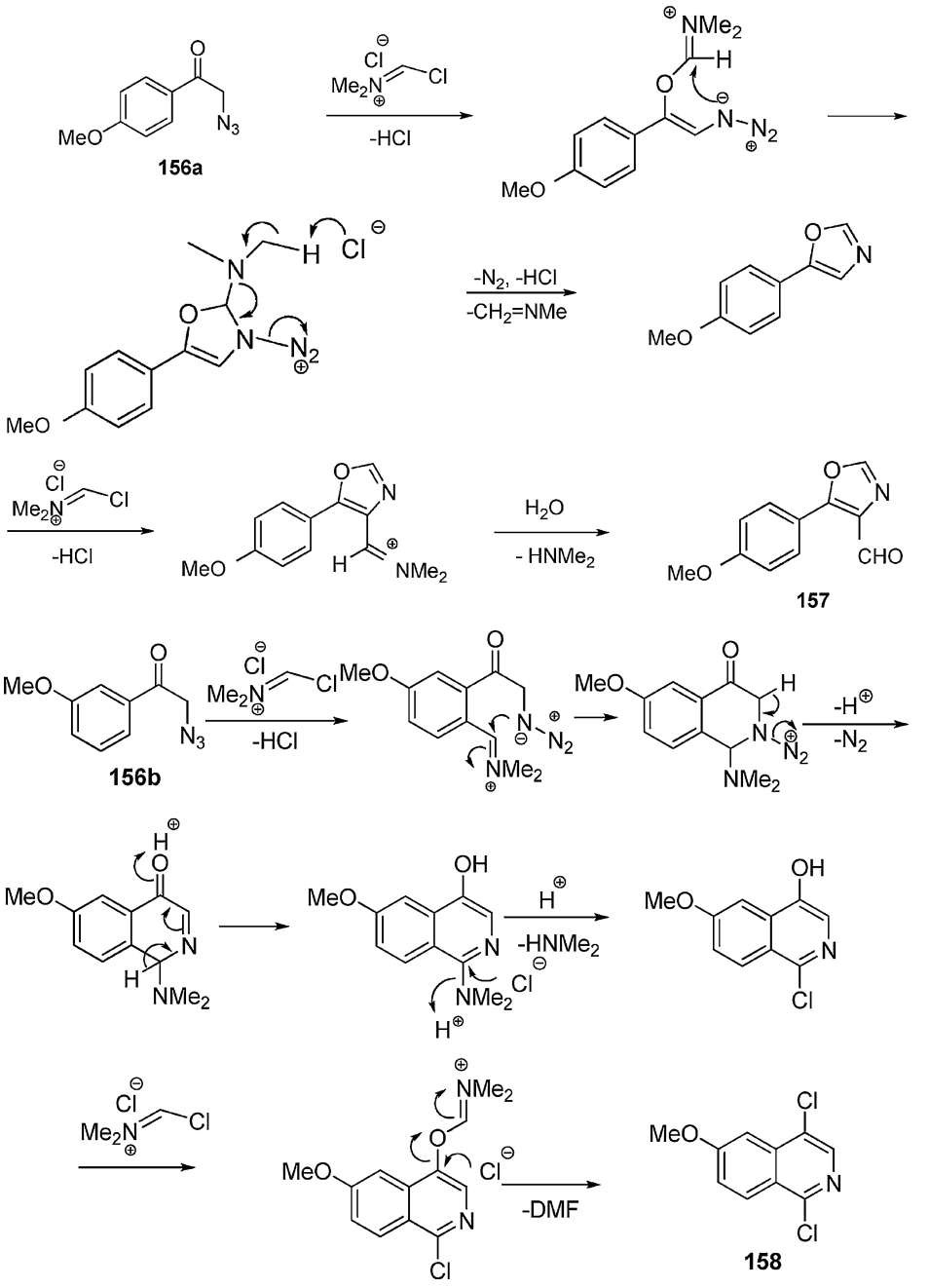
β-Haloamine 160. Typical Procedure.[191] *In an oven dried round bottom flask,the activated DMF complex (2 mmol) was prepared by adding the activating reagent (2 mmol) in DMF (1 mL) at 10°C. To this solution of N-tosylcyclohexylaziridine* **159** *(1 mmol) in DMF (0.5 mL) was added at the same temperature and the reaction mixture was allowed to warm to room temperature. After completion, the reaction mixture was added to ice-cold water and extracted with ethyl acetate. Work-up and purification by silica gel column chromatography gave the corresponding β-haloamine 160 in good to excellent yields.*

7. Beckmann Rearrangement

The Beckmann rearrangement reaction is a valuable method for synthesis of amides or nitriles from the corresponding oximes **161** by treatment with BTC/DMF, as shown in *Scheme 65*.[192] The possible mechanism indicated that the adduct **162** afforded the amides **163** upon hydrolytic workup in the case of ketoximes, directly affored the nitrile **164** in the case of aldoximes. Experimental results have shown that aryl ketoximes were more reactive than alkyl ketoximes and that electron-donating groups on the aromatic ring facilitated the reaction while electron-withdrawing groups retarded it. Moreover, aromatic aldoximes provided the corresponding nitriles in excellent yields.

8. Solid State Reactions

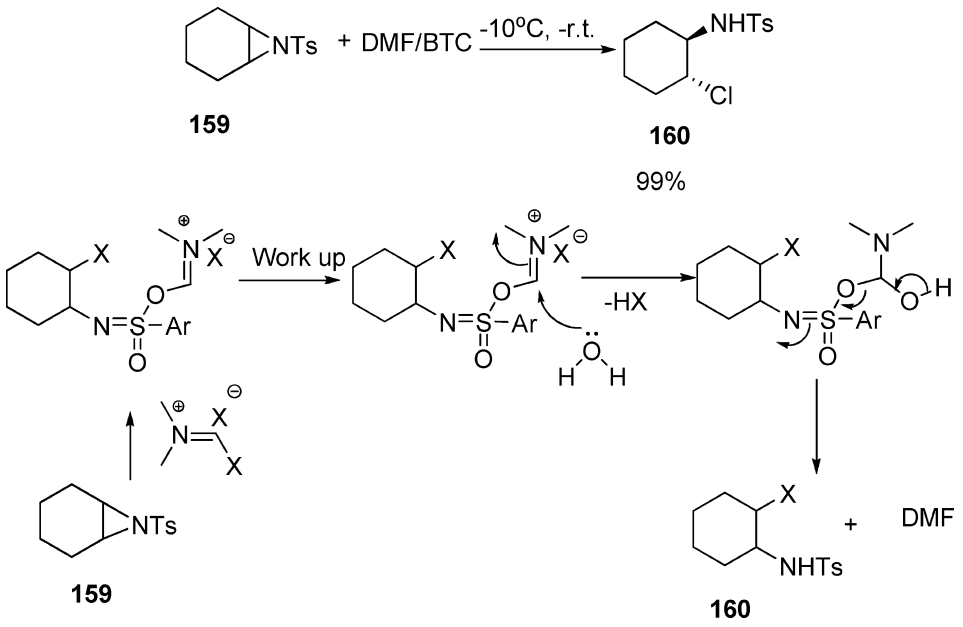
The earliest investigations into use of the Vilsmeier reagent on solid phase was by Tois *et al.*[144] in 2001. This methodology has the potential to be of great benefit in the convergent synthesis of a combinatorial library of thousands of compounds because of the merits of



Scheme 63

solid-phase synthesis, such as inherently time saving and reasonable purity of the final products without a significant purification step as in most solution phase chemistry.

In addition to the earlier studies, Rivero *et al.*[10] have outlined a simple method to generate a Vilsmeier type salt using resin-bound 1-*N*-piperazine-4-carboxaldehyde **167** in combination with BTC supported on solid phase (*Scheme 66*).



Scheme 64

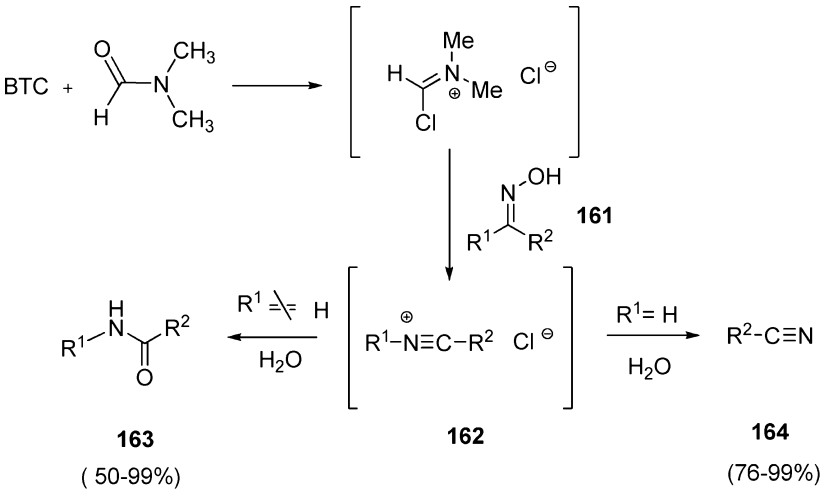
The activation process of several secondary formamides was first tested and piperazine **165** was selected finally because it contains two secondary amines: one of the amino groups can be attached to the resin, and the other can be formylated and then afford the supported Vilsmeier salt on treatment with BTC.

Various substrates such as *N*-methylpyrrole, pyrrole and 4-methylacetophenone were added to test the supported Vilsmeier salt which was swollen in $CHCl_3$. The formylation reaction was unimolecular and the supported salt **168** reacted with 1 equiv of the substrate such as *N*-methylpyrrole, pyrrole and 4-methylacetophenone. The ongoing reaction prevents secondary reactions involving more than one formylation, due to the relatively large intermolecular distances within the resin (>100 Å). Then the resin was hydrolyzed to obtain the corresponding aldehydes and the resin-1-*N*-piperazine **166**, which could be recovered and activated for further use.

Resin-bound 1-N-Piperazinylchloromethyliminium Chloride 168. Typical Procedure.[10] *In a round-bottom flask, resin-1-N-piperazine-4-carboxaldehyde* ***167*** *(0.81 g, 0.862 mmol), was swollen in acetonitrile for 30 min. The mixture was placed in an ice bath under inert atmosphere with a reflux system. A solution of BTC in acetonitrile was added dropwise (0.12 g, 0.40 mmol). The reaction mixture was allowed to react for 1 h at 50–60°C. The resin was filtered and washed with* CH_3CN*(3 × 30 mL) and* CH_2Cl_2 *(30 × 30 mL). This resin was used directly in the next step.*

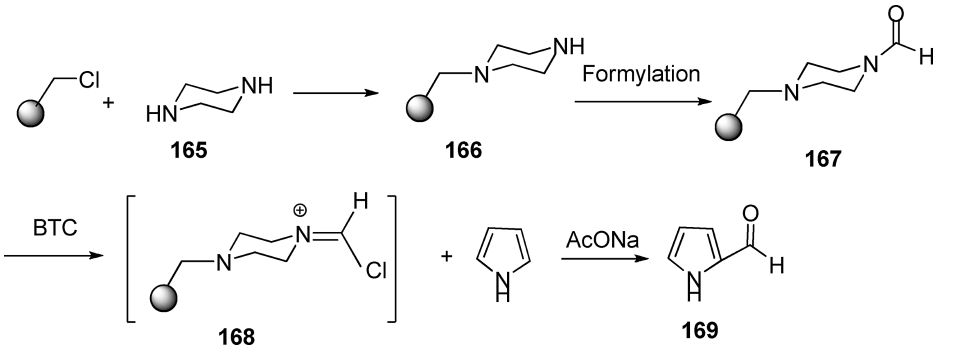
VII. Other Reactions

An efficient method has been developed for synthesis of dimethylaminomethylenediphosphonates (*Scheme 67*).[193] A class of inhibitors consists of the nitrogen-containing



a) $R^1 = C_6H_5$, $R^2 = CH_3$; b) R^1 =3-$O_2NC_6H_4$, $R^2 = CH_3$; c) R^1 = 4-$CH_3OC_6H_4$, $R^2 = CH_3$; d) R^1 =3-O_2N-4-CH_3-C_6H_3, $R^2 = CH_3$; e) R^1 = 2,5-Cl_2-4-F- C_6H_2, $R^2 = CH_3$; f) R^1 = 3-MeCONHC_6H_4, $R^2 = CH_3$; g) $R^1 = C_6H_5$, $R^2 = C_6H_5$; h) R^1 = 3-ClC_6H_4, $R^2 = C_2H_5$; i) R^1-R^2 = $(CH_2)_6$; j) R^1-R^2 = 1,2,3,4-tetrahydronaphthalen -1-yl; k) R^1 = 2-thienyl, $R^2 = CH_3$; l) R^1 = 2-furyl, $R^2 = CH_3$; m) R^1 = 4-$CH_3OC_6H_4$, R^2 = 4-ClC_6H_4; n) R^1 = iso-butyl, $R^2 = CH_3$; o) $R^1 = CH_3CH_2$, $R^2 = CH_3$; p) R^1 = H, R^2 =C_6H_5; q) R^1 = H, R^2 =3-$O_2NC_6H_4$; r) R^1 = H, R^2 =4-$MeOC_6H_4$; s) R^1 = H, R^2 = 4-ClC_6H_4; t) R^1 = H, R^2 = 4-$Me_2NC_6H_4$; u) R^1 = H, R^2 =2-Cl-6-F-C_6H_3; v) R^1 = H, R^2 =tert-amyl; w) R^1 = H, R^2 = cyclohexyl.

Scheme 65

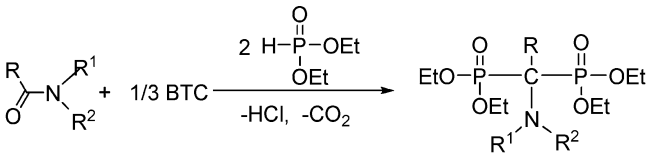


Scheme 66

bisphosphonates, such as pamidronate, alendronate, and risedronate, have been used in the treatment of bone resorption diseases.[194]

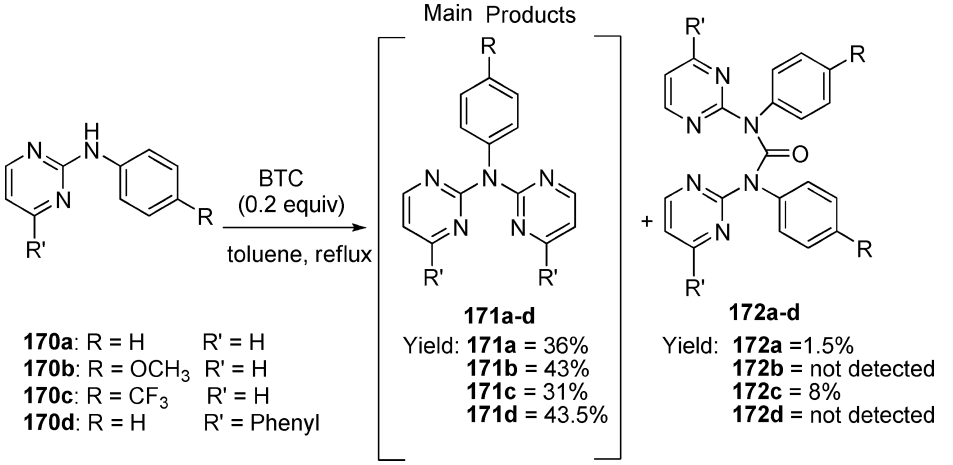
The yield was influenced by different substituents at the carbon atom in the linkage P-C-P. These results could be explained by consideration of steric hindrance. With the substrates containing the sterically crowding groups gave lower yields of products.

BTC has been used in some new reactions; noteworthy is the work of Prashad's group[195] for the synthesis of *N*-aryl-*N*-(2-pyrimidinyl)-2-pyrimidinamine. This group reported a new



a)R=H, $R^1 = CH_3$, $R^2 = CH_3$; b) R=CH_3; $R^1 = CH_3$, $R^2 = CH_3$; c) R=CH_3, $R^1 = C_2H_5$, $R^2 = C_2H_5$; d) R=CH_3, R^1 = Ph, R^2 = Ph; e) R = *n*-C_3H_7, R^1-R^2 = $(CH_2)_5$; f) R=$PhCH_2$, $R^1 = CH_3$, $R^2 = CH_3$; g) R = *n*-C_3H_7, $R^1 = C_2H_5$, $R^2 = C_2H_5$; h)R = *n*-C_3H_7, R^1-R^2 = $(CH_2)_2O(CH_2)_2$; i) R=Ph, R^1 = Ph, R^2 = Ph.

Scheme 67



Scheme 68

deamination-self amination reaction of *N*-aryl-2-pyrimidinamines with BTC in refluxing toluene to afford the target compounds (*Scheme 68*). Compounds **171a-f** were found to be the major products while very little of the excepted symmetrical urea products **172a-f** were obtained.

VIII. Conclusion and Outlook

As a versatile and inexpensive synthetic auxiliary, BTC has found extensive applications in the synthesis of drug intermediates[182] and pesticides.[15] In the past five years, the theory and application of BTC have been widely studied because of its contribution to limiting phosphorus pollution and also for providing mild reaction conditions. Many new utilizations of BTC for reaction with a number of substrates are being continuously developed. Our own laboratory is contributing to this effort. Extensive application of BTC-based chemistry to industrialized production can be expected in the near future.

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