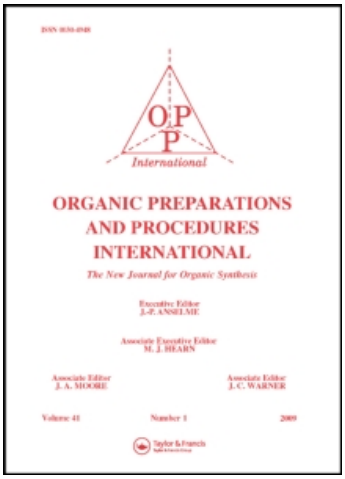

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NOVEL SYNTHETIC REACTIONS WITH 2-PYRIDYL RELATED REAGENTS. A REVIEW

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NOVEL SYNTHETIC REACTIONS WITH 2-PYRIDYL RELATED REAGENTS. A REVIEW

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INTRODUCTION

The development of efficient and reliable reagents for the activation of common functional groups such as carboxylic acids, alcohols, and amines is very important in organic synthesis. Various types of condensing agents have been recently developed for these purposes.[1]

Among several useful reagents derived from phosgene, 1,1'-carbonyldiimidazole first introduced by Staab[2], has enjoyed its role for the activation of alcohols, amines[3] and acids.[4] Bis-p-nitrophenyl carbonate[5] and bis-(8-quinolyl) carbonate[6] have been introduced in 1960's for the synthesis of p-nitrophenyl esters and for the protection of amino groups, respectively. The importance of active carbonates and active oxalates as condensing agents has been recognized in recent years. They include N,N'-disuccinimidyl carbonate,[7] diphthalimido carbonate,[8] 1,1'-(carbonyldioxy) dibenzotriazole,[9] N,N'-carbonyldi(1,2-benzisoxazole-3(2H)-one),[10] N,N'-disuccinimido oxalate,[11] 1,1'-oxalyldiimidazole[12] and 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] oxalate.[13] In general, they have been utilized for the preparation of carboxylic esters and amides by means of the activation of carboxylic acids.

We have been interested in the development of 2-pyridyl related reagents for the following reasons:

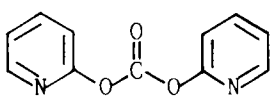
(i) Since 2-hydroxypyridine is an essentially neutral compound (pKa 0.75), it is possible that the desired reaction may take place under

essentially neutral conditions.

(ii) 2-Hydroxypyridine is water-soluble and the easy isolation of the products can be expected by the usual aqueous workup.

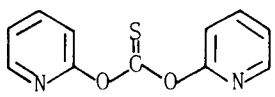
(iii) It was been reported that 2-pyridyl esters are considerably more reactive towards nucleophiles than p-nitrophenyl esters.[14] Thus, 2-pyridyl related reagents is expected to be reactive to become synthetically useful reagents.

On the basis of this information, we have prepared several 2-pyridyl related reagents derived from phosgene, thiophosgene and thionyl chloride and have investigated their synthetic utility. Furthermore, we have developed several synthetically useful reactions utilizing 2-pyridyl esters and S-2-pyridyl thioates. The present review mainly describes synthetically useful reactions using 2-pyridyl related reagents based on our previous results.



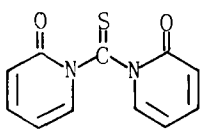
Di-2-pyridyl Carbonate

2-DPC



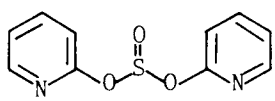
Di-2-pyridyl Thionocarbonate

DPT



1,1'-Thiocarbonyldi-2,2'-pyridone

Thiocarbonylbispyridone (TBP)



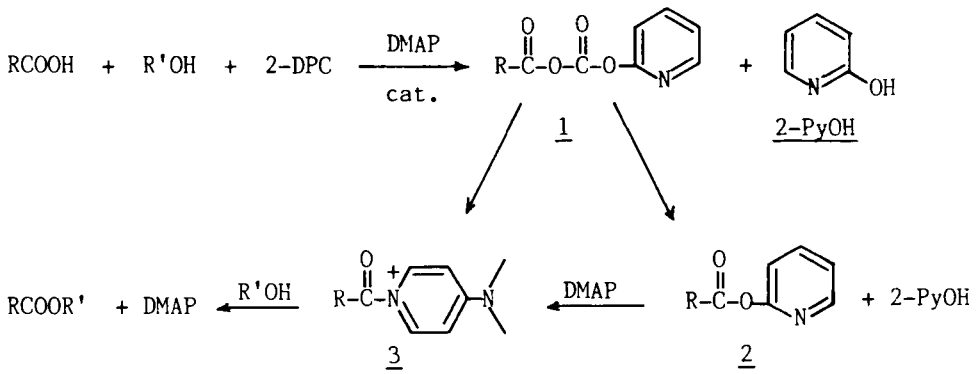
Di-2-pyridyl Sulfite

DPS

I. DEHYDRATION AND DEHYDROSULFURIZATION

1. Preparation of Esters

It has been reported that active carbonates such as N,N'-succinimidyl carbonate,[7] diphthalimido carbonate[8] and 1,1'-(carbonyldioxy)dibenzotriazole[9] have been utilized for the preparation of the corresponding



Scheme 1

active ester. However, these carbonates have not been generally used for the direct esterification of carboxylic acids, though carboxylic esters have been prepared by the alcoholysis of 1-benzotriazolyl related active esters using equimolar amounts of triethylamine or 4-dimethylaminopyridine (DMAP).[9,13,15]

The study of direct esterification of carboxylic acids using 2-DPC was initiated by the following observations as shown in Scheme 1.[16] (i) Carboxylic 2-pyridylcarbonic anhydrides (1), reactive acylating intermediates, should be rapidly produced by a nucleophilic attack of carboxylic anions on 2-DPC. (ii) It is expected that the intermediates (1) should be converted into 2-pyridyl esters (2) based on our previous results in DMAP[17] catalyzed esterification of carboxylic acids using mixed carboxylic-carbonic anhydrides.[18] (iii) The intermediate (1) can be directly converted into the desired esters in the presence of an alcohol via the intermediacy of N-acylpyridininium species (3), generated from nucleophilic attack of DMAP on carboxylic carbonyl center of the intermediate (1) and/or on 2-pyridyl esters (2), although the latter reaction should be much slower than the former.

On the basis of this information, the preparation of carboxylic esters from equimolar amounts of acids and alcohols using 2-DPC as a condensing agent was studied. Among several bases tested in this study, the use of a catalytic amount of DMAP gave the best results and is generally recommended. As shown in Table 1, most aliphatic acids, upon treatment with an equimolar mixture of alcohols and 2-DPC in the presence of 0.1 equiv of DMAP in dichloromethane at room temperature, gave the corresponding esters in high yields. However, the present method reaches a limit with aromatic acids, sterically hindered acids and hindered alcohols. In those cases, a mixture of alkyl esters and 2-pyridyl esters was obtained in variable ratios and the product composition was not significantly altered by the amount of DMAP and the reaction time. This method can be successfully applied for the preparation of thiol esters under the similar condition.

$$\text{RCOOH} + \text{2-DPC} \xrightarrow[\text{cat.}]{\text{DMAP}} \text{RCOO-2-Py} + \text{2-PyOH} \qquad (1)$$

$$\text{RCOOH} + \text{R'OH} + \text{2-DPC} \xrightarrow[\text{cat.}]{\text{DMAP}} \text{RCOOR'} + \text{2-PyOH} \qquad (2)$$

R'OH= HOSu, HOPt, HOBt, or HONp

It has been found that 2-DPC can be effectively used as a condensing agent for the preparation of various active esters such as 2-pyridyl, succinimido, phthalimido, benzotriazol-1-yl, and p-nitrophenyl.[19] When reactions were carried out with equimolar amounts of carboxylic acids and 2-DPC in the presence of 0.1 equiv of DMAP in dichloromethane at room temperature, the corresponding 2-pyridyl esters were obtained in high yields within 1 hr (Eq. 1). Furthermore, with equimolar amounts of the acid, 2-DPC, and the alcoholic component using N-hydroxysuccinimide (HOSu),

TABLE 1. Esterification of Carboxylic Acids with Alcohols[a]

$$RCOOH + R'OH \longrightarrow RCOOR'$$

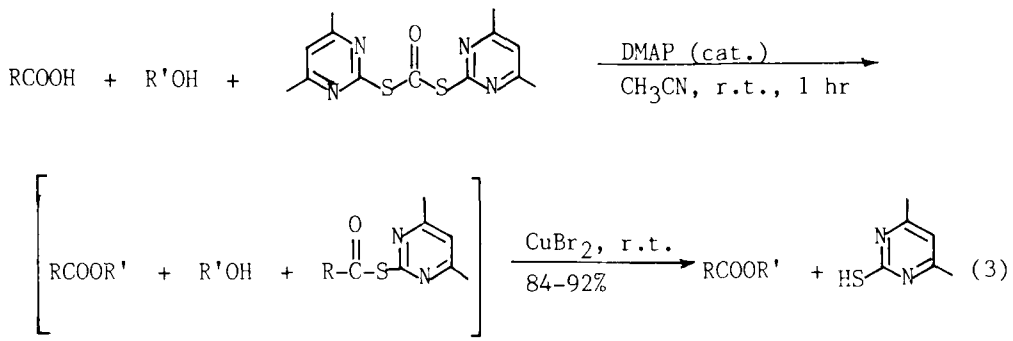
R	R'	Reagent	Time (hrs)	Yields of RCOOR'(%)[b]
$CH_3(CH_2)_6$	$C_6H_5CH_2$	2 DPC	2	4
		DPS	4	1
		DPTC	0.3	5
	CCl_2CH_2	2-DPC	0.5	91
		DPS	2	95
		DPTC	0.2	86
$C_6H_5CH_2$	$(CH_3)_2CH$	2-DPC	3	90
		DPS	24	81(9)
$(C_6H_5)_2CH$	$CH_2C_6CH_5$	2-DPC	1	92
		DPS	3	90
		DPTC	2.5	87
C_6H_5	C_2H_5	2-DPC	0.5	51(38)
		DPS	24	55(36)
$(CH_3)_3C$	$CH_2C_6H_5$	2-DPC	0.5	28(56)[c]
		DPS	0.3	58(23)[c]

[a] The reaction was carried out with equimolar amounts of acids, alcohols, and the reagent in the presene of 0.1 equiv of DMAP in dichloromethane at room temperature. [b] The numbers in parentheses indicate isolated yields of 2-pyridyl esters. [c] A small amount of pivalic anhydride (<8%) was isolated.

N-hydroxyphthalimide (HOPt), 1-hydroxybenzotriazole (HOBt), and p-nitrophenol (HONp) in the presence of 0.1 equiv of DMAP in dichloromethane at room temperature, the reaction was normally complete within 1 h to give satisfactory yields of the corresponding active esters (Eq. 2). Typical isolated yields were: MeCO-O-2-py, 90%; Boc-Leu-O-2-py, 81%; PhCO-OSu, 92%; Z-Phe-Osu, 87%; Z Leu-OPt, 88%; PhCO-OBt, 90%; Z-Leu-ONp, 85%; Boc-Ala-ONp,

78%.

Since the preparation of 2-DPC requires the use of highly toxic phosgene, we have prepared di-2-pyridyl sulfite (DPS) from thionyl chloride and 2-hydroxypyridine in the presence of triethylamine and studied the effectiveness of DPS in the esterification of carboxylic acids.[20] Although DPS is expected to be more reactive than 2-DPC, the reaction required slightly longer reaction times for completion of the reaction, indicating that more 2-pyridyl esters are formed. In general, the scope and limitations of the present method are very similar to those of the method using 2-DPC.



(3)

The effectiveness of S,S-bis(4,6-dimethyl-2-pyrimidinyl) dithiocarbonate (DPTC) has been studied as a condensing agent for the following reasons.[21] (i) The reagent should be more reactive than 2-DPC. (ii) The conversion of S-2-pyrimidinyl thioates into alkyl esters should be faster than that of 2-pyridyl esters. (iii) Copper ion promoted esterification of S-2-pyrimidinyl thioates should be much more faster than that of 2-pyridyl esters[22] and can be applied to the synthesis of carboxylic esters derived from aromatic acids, tertiary acids, and tertiary alcohols by the two-step procedure. As we expected, most carboxylic acids were prepared in high yields by the use of DPTC as shown in Table 1. Hindered esters of aromatic acids and tertiary acids could be prepared in high yields by the two-step

procedure (Eq. 3).

2. Preparation of Amides

A similar procedure utilized in the esterification proved unsuccessful for the direct preparation of amides from equimolar amounts of acids and amines, since competitive attack of amines on 2-DPC produced 2-pyridyl carbamates, causing the reaction to become complicated. However, this problem can be solved by a stepwise procedure. When acids were treated with 2-DPC and DMAP as a catalyst, 2-pyridyl esters were formed and subsequent treatment with amines provided carboxylic amides in high yields (Eq. 4).[23] Some typical isolated yields of amides were: $CH_3(CH_2)_6CONHCH_2C_6H_5$, 80%; C_6H_5CONH-c-C_6H_{11}, 85%; $(CH_3)_2CHCONHC_6H_5$, 86%.

$$RCOOH + 2\text{-DPC} \xrightarrow[\text{cat.}]{\text{DMAP}} R\text{-}\overset{\overset{O}{\|}}{C}\text{-O-2-Py} \xrightarrow{R'NH_2} R\text{-}\overset{\overset{O}{\|}}{C}\text{-NHR'} + 2\text{-PyOH} \qquad (4)$$

3. Preparation of Nitriles

a) From Aldoximes

Dehydration of aldoximes into nitriles using 2-DPC cleanly occurred in refluxing toluene and in the presence of an amine base in dichloromethane at room temperature (Eq. 5).[24] Among several bases tested in this study, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[25] gave the best results in terms of the rapidity and yield.

$$RCH{=}NOH + 2\text{-DPC (or TBP, DPS)} \longrightarrow R\text{-}C{\equiv}N \qquad (5)$$

As shown in Table 2, several aldoximes were cleanly converted into nitriles in high yields by using both procedures. The present reaction can also be accomplished with TBP[26] and DPS.[27] The reaction was complete

TABLE 2. Preparation of Nitriles

Compound	Reagent	Method[a]	Time (hrs)	Yield, %
$CH_3(CH_2)_7CH=NOH$	2-DPC	A	2	84
		B	12	84
	TBP	A	1	93
	DPS	A	0.2	93
$c\text{-}C_6H_{11}CH=NOH$	2-DPC	A	2	88
		B	12	87
	TBP	A	0.5	89
$C_6H_5CH=NOH$	2-DPC	B	3	83
	TBP	A	1	96
$p\text{-}CH_3O\text{-}C_6H_4CH=NOH$	2-DPC	A	0.5	82
	DPS	A	0.2	93
		C	24	83
$p\text{-}NO_2\text{-}C_6H_4CH=NOH$	2-DPC	A	0.5	90
		B	0.1	93
	TBP	A	1.5	90
$CH_3(CH_2)_6CSNH_2$	2-DPC	A	1	84
	TBP	A	1	88
	DPS	C	0.3	92
$C_6H_5CH_2CSNH_2$	TBP	A	1.5	95
	DPS	C	0.3	88
$p\text{-}CH_3\text{-}C_6H_4CSNH_2$	2-DPC	A	1	85
	TBP	A	1.5	94
	DPS	C	0.5	86
$p\text{-}CH_3\text{-}C_6H_4CONH_2$	DPS	A	1	87
$p\text{-}Br\text{-}C_6H_4CONH_2$	DPS	A	0.5	89
$p\text{-}CH_3O\text{-}C_6H_4CONH_2$	DPS	A	1	83

[a] Method A: in refluxing toluene. Method B: with 0.1 equiv of DBU in dichloromethane at room temperature. Method C: in dichlorometnane at room temperature.

within 30 min in refluxing toluene using DPS. TBP was very similar to 2-DPC in terms of reaction conditions and yields. Although a number of methods are available for this conversion,[28] the present method might become the method of choice for the conversion of aldoximes into nitriles because of its simplicity, effectiveness and mildness.

b) From Thioamides

Several thioamides were converted into nitriles using 2-DPC, TBP and DPS as dehydrosulfurization agents. The reaction was accomplished at room temperature within 30 min using DPS, while the reaction required several hours in refluxing toluene using 2-DPC and TBP. Some of the results are illustrated in Table 2.[23,26,27]

c) From Aromatic Amides

Aliphatic amides were inert to 2-DPC, DPT, TBP and DPS in refluxing toluene for several hours and the original amides were recovered unchanged.[23] However, aromatic amides were dehydrated to nitriles by DPS in refluxing toluene within 1 hr,[27] whereas they were inert to 2-DPC, DPT and TBP. Thus, the present method using DPS may be useful for selective conversion of aromatic amides into nitriles in the presence of aliphatic amides, although several methods for the conversion of amides into nitriles are available.[29]

4. Preparation of Isonitriles from Formamides

Dehydration of N-alkyl- or N-arylformamides represents the method of choice for the preparation of isonitriles. Among many dehydrating agents, application of phosgene[30] or diphosgene[31] in the presence of tertiary amines was found to be effective. While 2-DPC, TBP and DPT did not react with formamides under forcing conditions, it was found that DPS could be successfully used for the preparation of isonitriles from formamides.[27] The reaction was complete within 15 min in refluxing toluene using DPS. This method seems to be very attractive in terms of the rapidity, mildness,

and ease of isolation of the product. Typical isolated yields were: $C_6H_5CH_2$-N≡C, 82%; c-C_6H_{11} N≡C, 78%; p-CH_3O-C_6H_4-N≡C, 70%.

5. Preparation of Carbodiimides

Carbodiimides are particularly important condensing agents in the peptide synthesis and various methods for the preparation of carbodiimides from dehydrosulfurization of thioureas utilizing metal oxides and condensing agents have been developed.[32] Treatment of N,N'-disubstituted thioureas with DPT[33] or TBP[26] in the presence of DMAP in dichloromethane at room temperature or in refluxing toluene afforded the corresponding carbodiimides in high yields. However, it is noteworthy that N,N'-primary alkyl disubstituted thioureas did not undergo dehydrosulfurization to afford the corresponding carbodiimides using DPT and TBP under forcing conditions. However, dehydrosulfurization of thioureas with DPS occurred almost instantly and cleanly in dichloromethane at room temperature without the addition of DMAP.[27] This procedure is of quite general utility and N,N'-primary disubstituted thioureas were cleanly converted to the corresponding carbodiimides by the use of DPS. Typical isolated yields of carbodimides from thioureas using DPS were: C_6H_5-N=C=N-C_6H_5, 85%; C_6H_5-N=C=N-c-C_6H_{11}, 92%; c-C_6H_{11}-N=C=N-c-C_6H_{11}, 90%; n-C_4H_9-N=C=N-C_4H_9, 76%.

DPT and TBP were not effective in the dehydration of N,N'-disubstituted ureas to carbodiimides, although the reaction occurred to some extent under forcing conditions. Furthermore, it is noteworthy that DPS reacted with ureas to afford relatively unstable unknown products without the formation of the desired carbodiimides.[34]

III. CARBONYL AND THIOCARBONYL TRANSFER REACTIONS

1. Preparation of Isothiocyanates

The widely used method for the preparation of isothiocyanates involves the reaction of amines with carbon disulfide in the presence of a base to

form dithiocarbamate salts and their conversion into isothiocyanates can be often achieved by a variety of reagents. They include phosphoryl chloride,[35] DCC,[36] 2-chloropyridinium salts,[37] triphenylphosphine dibromide[38] and Grignard reagent.[39]

$$RNH_2 + \text{DPT or TBP} \xrightarrow[CH_2Cl_2]{\text{r.t.}} R\text{-}N{=}C{=}S \qquad (6)$$

Aliphatic and aromatic amines were directly converted to the corresponding isothiocyanates in high yields on treatment with DPT (Eq. 6).[33] The reaction most likely proceeds <u>via</u> 2-pyridyl thiocarbamates followed by rapid elimination of 2-hydroxypyridine at room temperature. The reaction was usually complete within 10 min at room temperature, though unreactive p-nitroaniline required 2 hrs using DPT. The use of TBP in this reaction required slightly longer reaction times for completion.[26] Since it is known that the action of N,N'-thiocarbonyldiimidazole with amines involves (1-alkyl- or arylthiocarbamoyl) imidazoles as intermediates, which can be thermally decomposed into isothiocyanates and imidazole,[40] while N,N'-thiocarbonyl-1,2,4-triazole results in the formation of stable (1-alkyl- or arylthiocarbamoyl)-1,2,4-triazole even with heating.[41] Thus the present method seems to be very attactive in terms of its simplicity, rapidity, mildness and high yields of products. Typical isolated yields of isothiocyanates from amines using DPT were: $C_6H_5CH_2NCS$, 90%; $(CH_3)_3CNCS$, 87%; $CH_2{=}CH\text{-}CH_2NCS$, 85%; C_6H_5NCS, 90%; $p\text{-}NO_2C_6H_4NCS$, 90%.

2. Preparation of Cyclic Carbonates and Cyclic Thionocarbonates

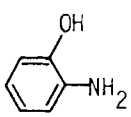
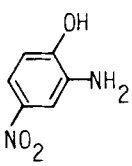
Cyclic carbonates, prepared from 1,2- and 1,3-diols and several carbonylating agents,[42] have been widely used for the protection of vicinal hydroxy groups. Cyclic carbonates are readily hydrolyzed under basic conditions, whereas they are relatively stable to acidic conditions.43

TABLE 3. Preparation of Cyclic Carbonates and Cyclic Thionocarbonates

Diols	Method[a]	Cyclic Carbonates Time, hrs	Yield,%	Cyclic Thionocarbonates Time, hrs	Yield, %
$CH_2(OH)-CH_2(OH)$	A	1	85	1	93
$CH_3CH(OH)CH_2CH_2(OH)$	A	1.5	83	1	91
	B	2.5	85	8	85
$C_6H_5CH(OH)-CH_2(OH)$	A	0.5	94	1	86
	B	1.5	83	4	87
$CH_2(OH)C(CH_3)_2CH_2(OH)$	B	3	90	4	95
$CH_2(OH)CH(C_2H_5)CH(n\text{-}C_3H_7)(OH)$	A	3	91	1	95
	B	10	94	16	96
$CH_3CH(OH)CH_2C(CH_3)_2(OH)$	A	1	89	4	88
	B	5	83		

[a] Method A: in refluxing toluene. Method B: in the presence of 0.1 equiv of DMAP in dichloromethane at room temperature.

Table 4. Preparation of 2-Oxazolidones and 2-Oxazolidinethiones in Dichloromethane at Room Temperature.

β-Aminoalcohol	2-Oxazolidones Time, min	Yield, %	2-Oxazolidinethiones Time, min	Yield, %
$CH_3CH(OH)-CH_2(NH_2)$	10	87	10	95
$CH_2(OH)-C(CH_3)_2(NH_2)$	5	96	10	93
$C_6H_5CH(OH)-CH_2(NH_2)$	10	93	10	90
	10	96	10	95
	60	96	10	92

When the cyclic carbonate formation was carried out in refluxing toluene using 1 equiv of 2-DPC, the reaction was normally complete within 3 hrs;[44] furthermore, this reaction could be carried out in the presence of 0.1 equiv of DMAP in dichloromethane at room temperature; triethylamine or pyridine were ineffective as catalysts. The present method is successful for the preparation of cyclic carbonates from structurally different 1,2- and 1,3-diols with the exception of sterically hindered bis-tertiary substituted diols as shown in Table 3. It is noteworthy that the use of N,N'-carbonyldiimidazole did not give satisfactory results with ethylene glycol and 1,3-butanediol, demonstrating the effectiveness of 2-DPC.

Similarly, synthetically useful cyclic thionocarbonates[45] were obtained in high yields under similar conditions using TBP.[28] The scope and limitations of TBP in the preparation of cyclic thionocarbonates were very similar to those of 2-DPC and the results are summarized in Table 3.

3. Preparation of 2-Oxazolidones and 2-Oxazolidinethiones

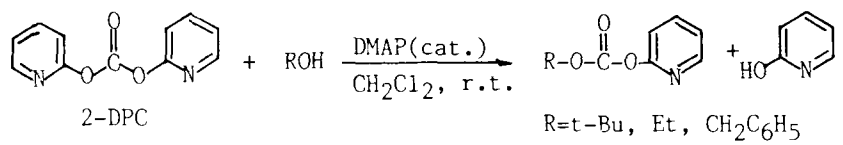
2-Oxazolidones and 2-oxazolidinethiones, important classes of heterocyclic compounds containing five-membered rings, are very useful in the synthesis of biologically active compounds and several methods for the preparation of 2-oxazolidones and 2-oxazolidinethiones have been reported.[46]

It was found that 2-DPC could be successfully used for the preparation of 2-oxazolidones from β-aminoalcohols. The reaction occurred almost instantly in dichloromethane at room temperature and was complete within 10 min, though the reaction required 1 hr in the case of relatively unreactive 2-amino-4-nitrophenol.[44] As shown in Table 4, 2-oxazolidinethiones could be prepared in high yields under similar conditions using TBP as a thiocarbonyl transfer reagent.[47]

III. ALKOXYCARBONYLATION

1. Preparation of Alkyl 2-Pyridyl Carbonates

Since a variety of active carbonates having t-butyl and benzyl group are well-known amino protective reagents in the peptide synthesis,[48] the reaction of alcohols with 2-DPC has been studied. Treatment of t-butanol with 2-DPC in the presence of 0.1 equiv of DMAP in dichloromethane at room temperature for 12 hrs afforded t-butyl 2-pyridyl carbonate in 80% yield (Eq. 7),[49] benzyl 2-pyridyl carbonate was also obtained in 70% yield in 2 hrs under similar conditions. Several alkyl 2-pyridyl carbonates were successfully prepared in the similar manner.



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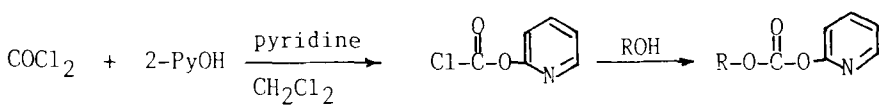
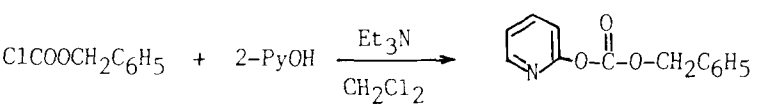


(8)



(9)

Furthermore, t-butyl 2-pyridyl carbonate could be prepared in 70% yield by the reaction of 2-pyridyl chloroformate (generated from phosgene, 2-hydroxypyridine and pyridine) with equimolar amounts of t-butanol and pyridine in dichloromethane (Eq. 8),[50] whereas benzyl 2-pyridyl carbonate could be easily prepared in 80% yield from benzyl chloroformate and 2-hydroxypyiridine (Eq. 9).[51]

2. Preparation of Carbamates and Ureas

t-Butyl 2-pyridyl carbonate was found to be very reactive toward amino acids.[50,51] Among solvents employed, aqueous dimethylformamide gave the best results in terms of the rapidity and the yield of the reaction. t-Butoxycarbonylation of amino acids was usually complete within 12 hrs at

room temperature and the corresponding N-Boc amino acids were obtained in high yields (Eq. 10). Some typical isolated yields of N-Boc amino acids were: N-Boc-Phe, 96%; N-Boc-Tyr, 88%; N-Boc-Met, 96%; N-Boc-Cys, 85%; N-Boc-Thr, 98%. Similarly, the benzyloxycarbonylation of amino acids with benzyl 2-pyridyl carbonate in aqueous dimethylformamide at room temperature occurred smoothly and rapidly.[51]

When 2-DPC was treated with several amines in dichloromethane at 0° for 4 hrs, the corresponding 2-pyridyl carbamates were obtained in high

$$RO\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}2\text{-}Py + H_2NCHR'COOH \xrightarrow[DMF\text{-}H_2O]{Et_3N} ROOC\text{-}NHCHR'COOH \quad (10)$$

R=t-Bu, benzyl

$$RNH_2 + 2\text{-}DPC \longrightarrow RNH\text{-}COO\text{-}2\text{-}Py \not\longrightarrow R\text{-}N{=}C{=}O + 2\text{-}PyOH \quad (11)$$

$$RNH\text{-}COO\text{-}2\text{-}Py + H_2O \xrightarrow[THF]{DMAP\ (cat.)} RNH\text{-}\overset{\overset{O}{\|}}{C}\text{-}NHR \quad (12)$$

$$RNH\text{-}COO\text{-}2\text{-}Py + R'NH_2 \longrightarrow RNH\text{-}\overset{\overset{O}{\|}}{C}\text{-}NHR' \quad (13)$$

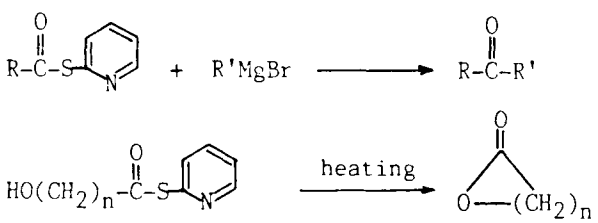
yields along with small amounts of the corresponding ureas (<5%) (Eq. 11).[49] It is noteworthy that the reaction did not afford the isocyanates and the 2-pyridyl carbamates obtained in this case did not thermally decompose into isocyanates and 2-hdyroxypyridine. Some typical isoalted yields of 2-pyridyl carbamates were: $CH_3CH_2CH_2NHCOO\text{-}2\text{-}Py$, 81%; $CH_3CH_2CH(CH_3$ NHCOO-2-Py, 82%; $c\text{-}C_6H_{11}NHCOO\text{-}2\text{-}Py$, 84%.

The reaction of 2-pyridyl carbamates with 0.1 equiv of DMAP in aqueous tetrahydrofuran did not give the original amines but the symmetrical ureas were obtained (Eq. 12).[49] The reaction proceeded cleanly at room temperature and required 12-24 hrs for completion of the reaction. Some typical isolated yields of the symmetrical ureas were: $C_6H_5CH_2NHCONHCH_2C_6H_5$, 90%; $CH_3CH_2CH_2NHCONHCH_2CH_2CH_3$, 92%; $c\text{-}C_6H_{11}NHCONHC_6H_{11}$, 95%.

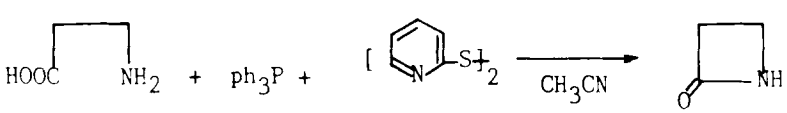
Unsymmetrical ureas could be conveniently prepared using 2-DPC by a two-step, one-pot procedure. 2-Pyridyl carbamates prepared from 2-DPC and amines were treated with equimolar amounts of amines to afford the corresponding unsymmetrical ureas in high yields (Eq. 13).[49] The reaction of 2-pyridyl carbamates with amines required 4 hrs at room temperature. Some typical isolated yields of unsymmetrical ureas were: $C_6H_5CH_2NHCONHC(CH_2CH_2CH_3)_2$, 81%; $CH_3CH_2CH(CH_3)NHCON(c\text{-}C_6H_{11})_2$, 87%; $c\text{-}C_6H_{11}NHCONH\text{-}n\text{-}C_4H_9$, 87%.

IV. SYNTHETICALLY USEFUL REACTIONS UTILIZING 2-PYRIDYL AND S-2-PYRIDYL ESTERS

S-2-pyridyl thioates and 2-pyridyl esters have attracted a great deal of attention in organic synthesis because of their versatile utility as acylating agents. As shown in Scheme 2, their synthetic utility have been previously demonstrated in the synthesis of peptides,[14] ketones,[52,53] and macrocyclic lactones.[54]



$$ROOCNHCHR^1COOH + NH_2CHR^2COOR^3 \xrightarrow{ph_3P,\ (Py\text{-}2\text{-}S\rightarrow)_2} ROOCNHCHR^1CONHCHR^2COOR^3$$

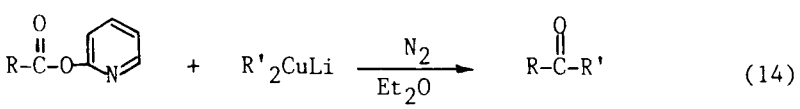


Scheme 2

S-2-pyridyl thioates have been conveniently prepared by employing oxidation-reduction condensation using triphenylphosphine and di-2-pyridyl disulfide[55] and an improved procedure has been developed by Corey and Clark using S-2-pyridyl chloroformate.[56] It is noteworthy that oxidation-reduction condensation utilizing triphenylphosphine and di-2-pyridyl disulfide has been found to be very useful in the synthesis of peptides[57] and β-lactams.[58]

1. Preparation of Ketones

Among many available synthetic methods on the synthesis of ketones from organometallic reagents and carboxylic acid derivatives,[59] the reaction of Grignard reagents with acid chlorides,[60] S-2-pyridyl thioates,[52] or 2-pyridyl esters[53] and of organocuprate reagents with acid chlorides[61] or thiol esters[62] are the most efficent and the most convenient. Furthermore, it has been reported that reaction of (β-allyl)nickel halides with 2-pyridyl esters affords α,β-unsaturated ketones.[63] Esters have been known to be generally inert to organocuprate reagents at -78°, although conversion of certain esters into ketones by using excess organocuprate reagents has been noted.[64] Since reaction of organocuprate reagents with 2-pyridyl esters has not been investigated, we have studied this reaction in detail (Eq. 14).[65] Reaction of lithium dialkylcuprates with 2-pyridyl esters in ether proceeded smoothly under nitrogen at -78°.



(14)

The reaction was usually complete within 2 hrs and the ketones were obtained in high yields. This reaction can be performed on 2-pyridyl esters having other sensitive functional groups such as bromide, ketones, and esters. Furthermore, it is noteworthy that the reaction can be done

with less than 1 equiv of the reagent, demonstrating complete utilization of both alkyl groups of lithium dialkylcuprates. This observation is in marked contrast to the results obtained from the reaction of organocuprate reagents with acid chlorides,[61] where 3 equiv of the reagent are required for optimal yields of ketones. Therefore, the reaction should proceed via lithium 2-pyridyloxyalkylcuprates. We have demonstrated that lithium 2-pyridyloxy-alkylcuprates (Eq. 15), generated from alkyllithium and 2-pyridyloxycopper, were stable at 0^{o} for 30 min with little decomposition according to Bertz procedure.[66] The reaction of acid chlorides with a stoichiometric amount of lithium 2-pyridyloxy(n-butyl)cuprate in THF at 0^{o} gave the corresponding ketones in high yields (Eq. 16).[67] Typical isolated yields of ketones were: n-C_7H_{15}CO-n-C_4H_9, 76%; c-C_6H_{11}CO-n-C_4H_9, 84%; $Br(CH_2)_6$CO-n-C_4H_9, 87%; $CH_3OOC(CH_2)_4$CO-n-C_4H_9, 84%.

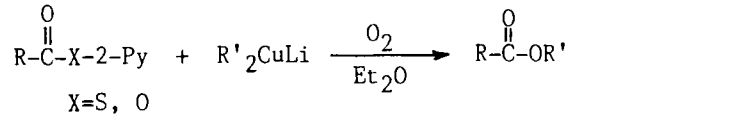
$$\text{2-PyOLi} + \text{CuI} \xrightarrow[\text{THF}]{} \text{2-PyOCu} + \text{LiI} \xrightarrow[\text{n-BuLi}]{} \text{(2-PyO)(n-Bu)CuLi} + \text{LiI} \qquad (15)$$

$$\text{RCOCl} + \text{(2-PyO)(n-Bu)CuLi} \longrightarrow \text{R-CO-n-Bu} \qquad (16)$$

The present method seems to be very attractive in terms of (i) stability of 2-pyridyl esters over other carboxylic acid derivatives used for the ketone synthesis, (ii) functional group specificity, (iii) an efficiency and yields and (iv) mildness of the reaction conditions.

2. Preparation of Esters via Oxidation of Dialkylcuprates

During the examination of the scope and limitations of the ketone synthesis using lithium dialkylcuprates with S-2-pyridyl thioates and 2-pyridyl esters, it was found that reaction of S-2-pyridyl thioates in the presence of oxygen with lithium dialkylcuprates surprisingly resulted in the formation of carboxylic esters free from ketones (Eq. 17)[67]. Similar results were obtained with 2-pyridyl esters.[65]

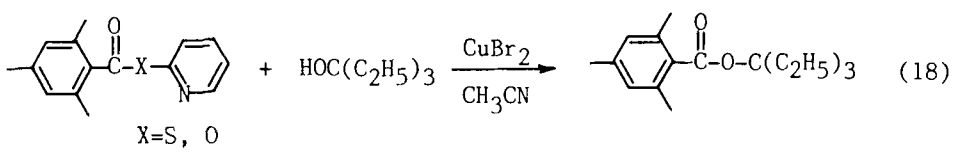


(17)

Although oxygen-containing products are obtained as byproducts from oxidation of many aryl copper reagents with oxygen, this observation is in marked contrast with previous reports that oxidation of organocuprates reagents with oxygen give the symmetrical coupling products.[6] It seems that the 2-pyridyl moiety is essential for the high-yield esters formation and the reaction proceeds via an intermediate copper alkoxide.

3. Preparation of Sterically Hindered Esters

Although a number of useful and reliable methods for the preparation of esters have been known, there are only a few methods available for the preparation of sterically hindered esters. These include the reaction of alcohols with the mixed anhydrides of carboxylic acids and trifluoroacetic anhydride,[70] of acid chlorides with lithium alkoxides,[71] and acid chlorides and alcohols with silver cyanide.[72] However, each method suffers from several problems such as harsh conditions and are limited in scope.



(18)

During the course of studying the synthetic utility of S-2-pyridyl thioates and 2-pyridyl esters, we observed that S-2-pyridyl mesitothioate was smoothly and rapidly esterified with equimolar amounts of t-butyl alcohol in the presence of cupric bromide in tetrahydrofuran at room temperature. After much experimentation, it was found that the combination of S-2-pyridyl thioates, cupric bromide, and acetonitrile as a solvent gave best results and is generally recommended for the preparation of hindered esters (Eq. 18).[22]

Employment of 0.5 and 1 equiv of cupric bromide resulted in the high yield formation of hindered esters at room temperature, whereas the reaction using 0.2 equiv of cupric bromide required a gentle heating for completion of the reaction of a short period of time. The present method was suitable for the preparation of a variety of aliphatic and aromatic hindered esters using sterically hindered aliphatic alcohols and aromatic alcohols.

Reaction using 2-pyridyl esters proceeded, compared with using S-2-pyridyl thioates, very slowly at room temperature and generally required gentle heating for completion of the reaction. Furthermore, it seems that 1 equiv of cupric bromide is required for this reaction to be a synthetically useful method for the preparation of hindered esters.

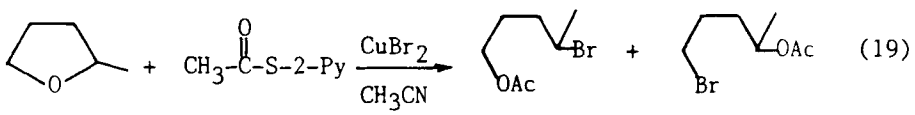
The present method appears to offer several advantages over previously known methods for the preparation of hindered esters with respects to (i) an efficiency (ii) yields, (iii) rapidity of the reaction, (iV) mildness, and (V) simple work-up and should find many useful applications in organic synthesis.

4. Facile Cleavage of Tetrahydrofuran Derivatives

While examining the mechanistic insights of the useful procedure for the preparation of hindered esters, we found that S-2-pyridyl thioate/cupric bromide rapidly and cleanly cleaved tetrahydrofuran derivatives in acetonitrile at room temperature,[73] although S-2-pyridyl thioate/cupric bromide was inert to tetrahydrofuran at room temperature for a long period of time in the absence of acetonitrile. Thus, the success of the reaction depended crucially on the use of acetonitrile as a solvent, although the reason for this observation is rather unclear.

When the reaction was carried out with equimolar amount of S-2-pyridyl methanethioate and cupric bromide using a slight excess of tetrahydrofuran derivatives in acetonitrile at room temperature, the reaction was normally

complete within 1 hr. Tetrahydrofuran and 2,6-dimethyltetrahydrofuran were cleanly cleaved into the corresponding bromoacetoxy derivatives in 80% and 75% isolated yield, respectively.



96 : 4 (19)

The present system showed a high regioselectivity in the cleavage of unsymmetrical tetrahydrofuran derivatives (Eq. 19). Thus, 2-methyltetrahydrofuran was converted into a mixture of 2-bromopentyl acetate and 5-bromo-2-pentylacetate in a ratio of 96:4, suggesting that the ring opening reaction may proceed via S_N1 process. The regioselectivity achieved with the present system is better than that obtained with the recently reported acetyl bromide/zinc chloride.[74] It is noteworthy that the present system did not cleave tetrahydropyan derivatives under forcing conditions but it readily cleaved epoxide derivatives. For instance, epibromohydrin was converted into a mixture of 2-acetoxy-1,3-dibromopropane and 1-acetoxy-2,3-dibromopropane in a ratio of 7:3 at room temperature within 20 min.

It is believed that the present system provides a useful alternative to currently available methods[75] in terms of mild condition and high regioselective cleavage of unsymmetrical tetrahydrofuran derivatives.

CONCLUSION

We have tried to review synthetically useful reactions utilizing 2-pyridyl and S-2-pyridyl moieties and emphasis was placed on new synthetic reactions with 2-pyridyl related reagents which have developed in our laboratory in recent years. The results which have been discussed here confirm the versatility and a general understanding of the chemical properties of 2-pyridyl related reagents. Although 2-pyridyl reagents such as 2-DPC, DPS, and TBP resemble previously known similar reagents derived

from imidazole, 1-hydroxybenzotriazole, and other appropriate heterocyclic compounds in many respects, 2-pyridyl related reagents have unique and characteristic chemical properties not present in other similar reagents and also have certain advantages over other similar reagents such as the wide aplicability, the mildness, the stability of the reagents, and the easy separation of the desired products. We strongly believe that 2-pyridyl related reagents should find many useful applications in oryanic synthesis.

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