1,1′-(Ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) as a recyclable catalyst for acylation

Sarala Naik[^], Veerababurao Kavala[^], Rangam Gopinath[^] and Bhisma K. Patel[^]*

Department of Chemistry, Indian Institute of Technology, Guwahati-781 039, India.
E-mail: patel@iitg.ernet.in

Abstract

1,1′-(Ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) catalyzes the acylation of structurally diverse alcohols, amines, thiols, and phenols with a variety of aliphatic and aromatic anhydrides. Steric factors in substrates as well as anhydrides and solvent play significant role during the formation of acylates. Chemoselective mono acetylation of symmetrical diols, primary hydroxy group over secondary and phenolic group and amines over phenols has been achieved. The compatibility of the protocol has been shown by the survival of different acid sensitive functionalities under the present reaction condition. The solvent, acetone, reacts with EDPBT giving bromoacetone and HBr, thus suppressing the bromination of substrates otherwise amenable to bromination. The reagent EDPBT being devoid of phase transfer property and owing to the high solubility of its precursor 1,1′-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB) in water, it was possible to isolate pure acylates by an aqueous work-up circumventing the need for further purification. The process is superior owing to the recyclability of the reagent. The spent reagent can be recovered, regenerated, and reused without any significant loss.

Keywords: Catalysis, alcohol, ester, amide, acylation, chemoselective, 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide

Introduction

The corrosive and toxic molecular bromine has recently been replaced by solid organic ammonium tribromides, because of the ease in their storage, transport, handling, and maintenance of desired stoichiometry.[1-7] These are unique reagents and have found diverse applications in recent years.[1-8] Their exploration as a source of anhydrous HBr makes the use of tribromides an attractive alternative to conventional protic and Lewis acids.[8] Notably, the acidity of the reaction medium using tribromides can be tuned by changing the polarity of the organic

[^] All authors have contributed equally

medium.[8e] To overcome the problem of recyclability, as is the case with most organic ammonium tribromides, we have recently reported a new reagent, 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) containing two tribromide units per molecule.[9] Unlike other tribromides, this reagent is devoid of phase-transfer property and can be recovered in significant amounts as its precursor 1,1′-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB) is highly water soluble. Taking into account the potential uses of tetrabutylammonium tribromide (TBATB) for different organic functional group transformations and the efficiency and recyclability of EDPBT, make further exploration of the reagent to other functional group transformations useful and viable.

Acylation of protic nucleophiles such as alcohols, amines, and thiols is an important and commonly used reaction in organic chemistry. The resulting esters, amides and thioesters serve as important functional components and / or intermediates in synthetic chemistry and biology.[10-12] In general acid anhydrides are employed as the acyl sources because of their ready availability and stability. Traditionally, bases such as triethylamine, pyridine, 4-(dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) and tributylphosphine (Bu_3P) are employed.[13-16] Because of their toxicity, flammability and unpleasant odors these bases are less attractive.[13] Acylation under acid catalyzed conditions has been reported with several reagents.[17,18] Metal triflates[19-29] and perchlorates[30-33] have been used for the purpose owing to their acidic nature. Other reagents / catalysts employed are TMSCl,[34] $HClO_4$-SiO_2,[35] $Sc(NTf_2)_3$,[36] Nafion-H,[37] Yttria-Zirconia,[38] distannoxane[15,39] heteropoly acid,[40] $MeSO_3H/Al_2O_3$,[41] solid surface-Al_2O_3,[42] and oxomolybdenum species.[43] Although metal triflates, perchlorates and other acidic catalysts are effective for the acylation reaction, their use is limited due to explosive nature of metal perchlorates and strong acidic character of triflates which results in side reactions. The drawbacks associated with some of the procedures reported in literature are arduous preparation of catalysts, difficulties in work-up and isolation, the need for an inert atmosphere, harsh reaction conditions, expensive reagents, low yields, longer reaction times, dry solvents and incompatibility with other protecting groups. In this context search for achieving general nucleophilic acyl substitution of anhydrides in a catalytic, mild fashion with integrity of existing acid and base sensitive functionalities remains in great demand. Though a plethora of reagents and procedures for acylation have been documented in the literature, need to find an efficient and mild acylation reaction still remains. Herein, we reveal a new, mild procedure for preparation of various esters, amides and thioesters with a variety of aliphatic and aromatic anhydrides in the presence of catalytic quantity of EDPBT.

Results and Discussion

Initially 3-phenyl propanol **3** (5 mmol) was taken as the model substrate for acetylation and was reacted with acetic anhydride (6.25 mmol) in a donor solvent such as acetonitrile (10 mL) in the presence of catalytic quantity of EDPBT (0.25 mmol). Progress of the reaction was monitored using thin layer chromatography, which showed complete conversion of the alcohol to its acetate

within 35 min. Earlier we have reported that the acidity of the reaction medium employing tribromides can be tuned by changing the polarity of the solvent.[8] So using this fact; the reaction was performed in different solvents such as toluene, methylene chloride, chloroform and acetone. When 3-phenyl propanol **3** was reacted with acetic anhydride in the presence of EDPBT in above solvents separately, it was observed that the reaction proceeded much faster in acetone compared to other solvents. This could be due to the reaction of acetone with EDPBT forming bromoacetone and thereby generating anhydrous HBr *in situ*, which catalyzes the reaction. In a control experiment treatment of the reaction mixture with a catalytic quantity of bromine and aq.HBr instead of EDPBT in acetone yielded 95% and 88% of acylated product respectively within 10 minutes. The summary of the solvent dependent study is shown in Table 1. This result prompted us to use acetone as the reaction medium.

Table 1. Solvent dependent acylation of 3-phenyl propanol (**3**)

Substrate	Solvent	Time/min	Yield (%)[a]
$PhCH_2CH_2CH_2OH$ (**3**)	Toluene	90	88
	CH_2Cl_2	60	91
	CH_3CN	35	93
	CH_3COCH_3	05	95
$PhCH(CH_3)OH$ (**16**)	Toluene	120	80
	CH_2Cl_2	75	86
	CH_3CN	50	92
	CH_3COCH_3	15	93

[a]GC yield

The reagent and the methodology are superior with respect to other conventional reagents as it results in a highly efficient acetylation of 3-phenyl propanol **3** (Table 2). Summary of the acetylation using 0.05 equivalents of different reagents employing acetone as the solvent is shown in Table 2. It may be noted that the yields reported in Table 2 are much lower than those has been reported in the literature, a possible reason could be the use of different amounts of catalyst, acetic anhydride and solvent system.

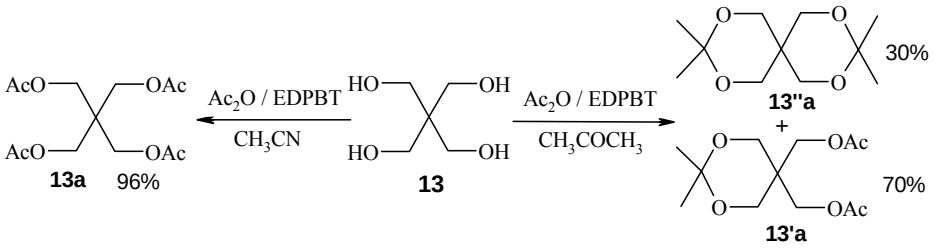
Under the present optimized reaction condition, diverse arrays of alcohols were converted to their respective acetates (Table 3). Aliphatic primary alcohols **1**-**3** were transformed to their corresponding acetates in excellent yields in a short time. Benzylic alcohols with deactivated substituents in the aromatic ring **4-5** were also acetylated efficiently. By employing this reagent we carried out acetylation of hindered and deactivated benzylic alcohol **6** in excellent yield but with a longer reaction time 24 h. However, other hindered alcohols **7-8** underwent acetylation smoothly giving product in excellent yield. Primary aliphatic diols **9-12** were diacetylated completely with acetic anhydride (2.5 equiv.). When pentaerythritol **13**, a substrate containing four symmetrical hydroxyl groups, was reacted with acetic anhydride (5 equiv.) it gave a

diisopropylidine derivative **13″a** along with the isopropylidine diacetate **13′a** in the ratio (30:70). It is worth noting that a change of solvent from acetone to acetonitrile resulted in the formation of pentaerythritol tetraacetate **13a** as the sole product in nearly quantitative yield (96%), Scheme 1.

Table 2. Acetylation of 3-phenyl propanol **3** in acetone using 0.05 equiv. of the reagents and acetic anhydride (1.25 equiv.)

Substrate	Reagents used	Time/h	Yield (%)[a]
$PhCH_2CH_2CH_2OH$ (**3**)	$ZnCl_2$	24	30
	$CoCl_2$	24	35
	$MgBr_2$	24	40
	$RuCl_3$	24	70
	NBS	8	92
	$Cu(OTf)_2$	24	55
	$LiClO_4$	24	60
	$HClO_4$-SiO_2,	24	30
	EDPBT	0.25	98

[a]GC yield



Scheme 1. Acetylation and isopropylidination of pentaerythritol **13**.

Secondary alicyclic alcohol such as cyclohexanol **14** was converted to its acetate in good yield. It was gratifying to observe that menthol **15** was completely converted to menthyl acetate **15a** with 1.25 equiv of Ac_2O within 10 min, an earlier work has reported that it was acetylated in 1.5 h at 0°C with 5 equivalents of Ac_2O in the presence of 1 mol% of $Bi(OTf)_3$.[21] Benzylic secondary alcohols such as **16-19** underwent acetylation smoothly but with a slightly longer reaction time as compared to their primary analogues. However, the scope of acetylation is somewhat limited for hindered aromatic secondary alcohol 9-fluorenyl alcohol **20**, which took 5 h for complete conversion under reflux. The results obtained have been summarized in Table 3.

Table 3. Acetylation[a] of alcohols with Ac_2O catalyzed by EDPBT in acetone

Substrate	Product	Time/min	Yield (%)[b]
$CH_3(CH_2)_8CH_2OH$ (**1**)	$CH_3(CH_2)_8CH_2OAc$ (**1a**)	5	92
$CH_3(CH_2)_{10}CH_2OH$ (**2**)	$CH_3(CH_2)_{10}CH_2OAc$ (**2a**)	5	93
$Ph(CH_2)_2CH_2OH$ (**3**)	$Ph(CH_2)_2CH_2OAc$ (**3a**)	5	95
3-NO_2-C_6H_4-CH_2OH (**4**)	3-NO_2-C_6H_4-CH_2OAc (**4a**)	15	90
4-Cl-C_6H_4-CH_2OH (**5**)	4-Cl-C_6H_4-CH_2OAc (**5a**)	10	92
2-Cl-6-NO_2-C_6H_3-CH_2OH (**6**)	2-Cl-6-NO_2-C_6H_3-CH_2OH (**6a**)	24h	80
9-Flurenyl-CH_2OH (**7**)	9-Flurenyl-CH_2OAc (**7a**)	10	95
$(PhCH_2)_2N(CH_2)_2OH$ (**8**)	$(PhCH_2)_2N(CH_2)_2OAc$ (**8a**)	10	92
$HO(CH_2)_5OH$ (**9**)	$AcO(CH_2)_5OAc$ (**9a**)	10	89[c]
$HOCH_2CH_2OCH_2CH_2OH$ (**10**)	$AcOCH_2CH_2OCH_2CH_2OAc$ (**10a**)	10	90[c]
$HOCH_2C(CH_3)_2CH_2OH$ (**11**)	$AcOCH_2C(CH_3)_2CH_2OAc$ (**11a**)	10	90[c]
3-Chloro-1,2-propane diol (**12**)	1,2-Diacetoxy-3-chloro propane (**12a**)	10	90[c]
$C(CH_2OH)_4$ (**13**)	$(AcOCH_2)_2C[(CH_2O)_2C(CH_3)_2]$ (**13′a**)	60	70[d]
$C(CH_2OH)_4$ (**13**)	$C(CH_2OAc)_4$ (**13a**)	5h	96[e]
Cyclohexanol (**14**)	Cyclohexyl acetate (**14a**)	10	85
Menthol (**15**)	Menthyl acetate (**15a**)	10	87
C_6H_5-$CH(CH_3)OH$ (**16**)	C_6H_5-$CH(CH_3)OAc$ (**16a**)	15	92
3-NO_2-C_6H_4-$CH(CH_3)OH$ (**17**)	3-NO_2-C_6H_4-$CH(CH_3)OAc$ (**17a**)	35	84
4-Cl-C_6H_4-$CH(CH_3)OH$ (**18**)	4-Cl-C_6H_4-$CH(CH_3)OAc$ (**18a**)	35	89
$(C_6H_5)_2CHOH$ (**19**)	$(C_6H_5)_2CHOAc$ (**19a**)	30	89
9-Fluorenyl-OH (**20**)	9-Fluorenyl OAc (**20a**)	5h	79[f]

[a]Reactions were monitored by TLC. [b]Isolated yield. [c]2.5 equivs. of Ac_2O were used. [d]5 equivs. of Ac_2O were used in acetone.[e]5 equivs. of Ac_2O were used in CH_3CN. [f]Reflux condition.

This methodology was also successfully applied to a representative variety of functionalized alcohols (Table 4). Diacylated product was obtained without affecting the multiple bonds in substrates, but-2-ene-1,4-diol **21** and but-2-yne-1,4-diol **22** with acetic anhydride (2.5 equiv.). Cholesterol **23** took comparatively longer reaction time for the transformation. A substrate containing two hydroxyls and a NHBoc functionality **26** gave monoacylated product without affecting the NHBoc group when reacted with acetic anhydride (1.25 equiv.). The present method is also effective for acylation of α,β-unsaturated alcohol such as cinnamyl **24**. Conversion of 4-allyloxy benzyl alcohol **25** to its acetate also occurred smoothly without affecting the double bond. Moreover, substrates bearing acid sensitive groups such as NHBoc **26**, OMe **27**, THP **28**, and TBS ether **31**, and base sensitive groups such as benzoate **29-30** remained intact under the described reaction condition revealing the functional group compatibility. The pKas of HBr, $HClO_4$ and triflic acid respectively are –9, -10, and –13 showing that triflic and perchloric acids have stronger acidic character compared to HBr. It may

be noted that strong Lewis acid character of metal triflates makes them unsuitable for acid-sensitive substrates. In scandium triflate catalyzed acetylation, rearranged products of allylic alcohols have been observed.[24d] Results obtained for differential functionalized alcohols have been summarized in Table 4.

Table 4. EDPBT catalyzed acetylation[a] of functionalized alcohols in acetone

Substrate	Product	Time/min	Yield (%)[b]
$HOCH_2CH=CHCH_2OH$ (**21**)	$AcOCH_2CH=CHCH_2OAc$ (**21a**)	60	84[c]
2-Butyne-1,4-diol (**22**)	1,4-Diacetoxy-2-butyne (**22a**)	75	86[c]
Cholesterol (**23**)	Cholesteryl acetate (**23a**)	8h	90
$PhCH=CH-CH_2OH$ (**24**)	$PhCH=CH-CH_2OAc$ (**24a**)	05	89
4-Allyloxy-C_6H_4-CH_2OH (**25**)	4-Alloylloxy-C_6H_4-CH_2OAc (**25a**)	20	90
$OHCH_2C(CH_3,NH(Boc)CH_2OH$ (**26**)	$AcOCH_2C(CH_3,NH(Boc)CH_2OH$ (**26a**)	90	70
4-OMe-C_6H_4-CH_2OH (**27**)	4-OMe-C_6H_4-CH_2OAc (**27a**)	10	92
$THPO(CH_2)_5CH_2OH$ (**28**)	$THPO(CH_2)_5CH_2OAc$ (**28a**)	10	87
C_6H_5-$COOCH_2CH_2OH$ (**29**)	C_6H_5-$COOCH_2CH_2OAc$ (**29a**)	30	92
C_6H_5-$COO(CH_2)_2OCH_2CH_2OH$ (**30**)	C_6H_5.$COO(CH_2)_2OCH_2CH_2OAc$ (**30a**)	40	94
4-OTBDMs-C_6H_4-CH_2CH_2OH (**31**)	4-OTBDMs-C_6H_4-CH_2CH_2OAc (**31a**)	60	85

[a]Reactions were monitored by TLC. [b]Isolated yield. [c]2.5 equivs of Ac_2O were used.

The acetylation of a wide range of structurally varied aliphatic, benzylic, allylic alcohols and phenols highlight the fact that the method is capable of generalization. However, phenols were sluggish under the present reaction condition and took comparatively longer reaction time for completion (Table 5). This result was attributed to the differential nucleophilicities of phenols and aliphatic alcohols under the reaction condition. It is noteworthy to quote that phenols are less nucleophilic than aliphatic alcohols under acidic condition but more nucleophilic under basic condition.[24b] Phenols containing electron donating groups in the aromatic ring **33-35** were acetylated with ease in comparison to those with electron-withdrawing groups **36-37** (Table 5).

Numerous procedures have been reported in literature for acylation of amines.[10,48,49] Some of the catalysts that are capable of acylating alcohols, phenols, thiols and amines are $RuCl_3$,[18e] $InCl_3$,[18f] $BiOClO_4$,[33] heteropoly acid,[40] solid surface-Al_2O_3,[42] oxomolybdenum species,[43] $V(O)(OTf)_2$.[44] The versatility of the described procedure can be observed from its successful application to N- and S-acylation of structurally different amines and thiols. Primary aromatic amines **38-40** and anilines with various substituents **41-44** were converted to their corresponding amides in short time, whereas secondary amine **45** took hours for completion. This result is not surprising since N-acylation of primary amines has been carried out without the use of any acidic or basic catalyst.[50] Thioacetal and hemithioacetal were obtained as side products when acylation of dodecanethiol **46** was carried out in acetone. However, the corresponding thioacetate was obtained by changing the solvent to acetonitrile. The results have been summarized in Table 5.

Table 5. Acetylation[a] of phenols, amines and thiols with Ac_2O catalyzed by EDPBT

Substrate	Product	Time / min	Yield (%)[b]
C_6H_5-OH (**32**)	C_6H_5-OAc (**32a**)	5h	80
2-Me-C_6H_4-OH (**33**)	2-Me-C_6H_4-OAc (**33a**)	3h	82
4-OH-C_6H_4-OH (**34**)	4-OAc-C_6H_4-OAc (**34a**)	5h	85
2-OH-C_6H_4-OH (**35**)	2-OAc-C_6H_4-OAc (**35a**)	5h	78
4-NO_2-C_6H_4-OH (**36**)	4-NO_2-C_6H_4-OAc (**36a**)	24h	25
4-CN-C_6H_4-OH (**37**)	4-CN-C_6H_4-OAc (**37a**)	24h	15
$CH_3(CH_2)_2CH_2NH_2$ (**38**)	$CH_3(CH_2)_2CH_2NHAc$ (**38a**)	05	80
C_6H_5-CH_2-NH_2 (**39**)	C_6H_5-CH_2-NHAc (**39a**)	05	89
Ph-$CH(CH_3)NH_2$ (**40**)	Ph-$CH(CH_3)$NHAc (**40a**)	05	85
$C_6H_5NH_2$ (**41**)	C_6H_5NHAc (**41a**)	05	95
4-Me-C_6H_4-NH_2 (**42**)	4-Me-C_6H_4-NHAc (**42a**)	05	92
2-F-C_6H_4-NH_2 (**43**)	2-F-C_6H_4-NHAc (**43a**)	05	90
4-NH_2-C_6H_4-NH_2 (**44**)	4-NHAc-C_6H_4-NHAc (**44a**)	05	92
$(C_6H_5)_2NH$ (**45**)	$(C_6H_5)_2$NAc (**45a**)	16h	75
$CH_3(CH_2)_{10}CH_2SH$ (**46**)	$CH_3(CH_2)_{10}CH_2SAc$ (**46a**)	60	70[c]

[a] Reactions were monitored by TLC. [b]Isolated yield. [c] CH_3CN was used as the solvent.

The marginal difference in acylation rate between primary and secondary alcohols, particularly for diols containing both types of hydroxyl yields substantial amount of diacylate.[51a] Selective monoacylation of symmetrical as well as unsymmetrical diols with various reagents using symmetrical anhydrides have been reported.[15,21e,23b,25,27,39-42,51] High selectivity was obtained for unsymmetrical aliphatic diol possessing both primary and secondary hydroxyl groups such as 1,3-butanediol **47** when the present method was employed. The primary hydroxyl group was selectively acetylated prior to secondary one with lot wise addition of acetic anhydride (1.2 equiv.) in the presence of EDPBT (0.05 equiv) in acetone. However, lower selectivity was observed for symmetrical primary diols **9** and **21** even with lot wise addition of the anhydride. The ratios of mono and diacetylated product obtained for substrates pentane-1,5-diol **9** and but-2-ene-1,4-diol **21** were respectively 65:25 and 75:20. The poor reactivity of phenols with acetic anhydride in presence of EDPBT raised a genuine possibility of selective acylation of aliphatic alcohols over phenols. For substrate **48** containing both primary and phenolic hydroxyl group, selective monoacetylation occurred at the aliphatic hydroxyl giving exclusively monoacetylated product **48a**. Substrate *p*-aminophenol **49** produced the corresponding acetamide; without affecting the phenolic group. Selective N-acetylation is of significant interest for the preparation of the antipyretic and analgesic drug paracetamol **49a.** Results obtained have been summarized below in Table 6.

Table 6. Selective monoacetylation[a] of diols with Ac_2O catalyzed by EDPBT in acetone

Substrate	Product	Time / min	Yield (%)[b]
$HOCH_2(CH_2)_3CH_2OH$ (**9**)	$HOCH_2(CH_2)_3CH_2OAc$ (**9'a**)	05	65
	$AcOCH_2(CH_2)_3CH_2OAc$ (**9a**)		25
$HOCH_2$-CH=CH-CH_2OH (**21**)	$HOCH_2$-CH=CH-CH_2OAc (**21'a**)	30	75
	$AcOCH_2$-CH=CH-CH_2OAc (**21a**)		20
$HO(CH_2)_2CHOHCH_3$ (**47**)	$AcO(CH_2)_2CH(OH)CH_3$ (**47'a**)	10	80
	$AcO(CH_2)_2CH(OAc)CH_3$ (**47a**)		15
4-OH-C_6H_4-CH_2CH_2OH (**48**)	4-OH-C_6H_4-CH_2CH_2OAc (**48a**)	10	85
	4-OAc-C_6H_4-CH_2CH_2OAc (**48'a**)		00
4-OH-C_6H_4-NH_2 (**49**)	4-OH-C_6H_4-NHAc (**49a**)	05	90
	4-OAc-C_6H_4-NHAc (**49'a**)		00

[a] Reactions were monitored by TLC. [b] Isolated yield

There are few reports of pivaloylation, benzoylation and acylation using other anhydride and alcohols.[19,21,24,43] It is worth noting that none of the procedures reported in literature has focused on the acylation of alcohols, amines, and thiols with isobutyric anhydride. In order to extend the scope of the methodology, acylation of alcohols, amines, and thiols with other anhydrides was carried out under the identical condition as described using acetic anhydride. A variety of aliphatic and aromatic alcohols (**1, 3, 16, 24**), amine **41** and thiol **46** were propionylated using propionic anhydride. Chemoselective propionylation of primary alcohol over phenol, and amine over phenol could be observed as demonstrated for substrates **48** and **49** respectively as shown in Table 7.

Table 7. Propionylation[a] of alcohols, thiol and amines with $(EtCO)_2O$ catalyzed by EDPBT

Substrate	Product	Time / min	Yield (%)[b]
$CH_3(CH_2)_8CH_2OH$ (**1**)	$CH_3(CH_2)_8CH_2OCOEt$ (**1b**)	15	88
$Ph(CH_2)_2CH_2OH$ (**3**)	Ph-$(CH_2)_2CH_2OCOEt$ (**3b**)	15	94
Ph-$CH(CH_3)OH$ (**16**)	Ph-$CH(CH_3)OCOEt$ (**16b**)	30	90
$PhCH=CHCH_2OH$ (**24**)	$PhCH=CHCH_2OCOEt$ (**24b**)	15	93
C_6H_5-NH_2 (**41**)	C_6H_5-NHCOEt (**41b**)	05	95
$CH_3(CH_2)_{10}CH_2SH$ (**46**)	$CH_3(CH_2)_{10}CH_2SCOEt$ (**46b**)	60	72[c]
4-OH-C_6H_4-CH_2CH_2OH (**48**)	4-OH-C_6H_4-CH_2CH_2OCOEt (**48b**)	10	82
4-OH-C_6H_4-NH_2 (**49**)	4-OH-C_6H_4-NHCOEt (**49b**)	10	96

[a] Reactions were monitored by TLC. [b] Isolated yield. [c] CH_3CN was used as the solvent

Other anhydrides such as isobutyric and pivalic reacted successfully as shown in Table 8 and 9 respectively. It is needless to mention that chemoselective isobutyrylation and

pivaloylation of primary alcohol over phenol was observed as demonstrated for substrate **48** (Table 8 and 9).

Table 8. Isobutyrylation[a] of alcohols, thiol and amines with $(iPrCO)_2O$ catalyzed by EDPBT

Substrate	Product	Time/min	Yield (%)[b]
CH_3-$(CH_2)_8CH_2OH$ (**1**)	CH_3-$(CH_2)_8CH_2OCOiPr$ (**1c**)	20	89
Ph-$(CH_2)_2CH_2OH$ (**3**)	Ph-$(CH_2)_2CH_2OCOiPr$ (**3c**)	20	92
Ph-$CH(CH_3)OH$ (**16**)	Ph-$CH(CH_3)OCOiPr$ (**16c**)	30	88
$PhCH=CHCH_2OH$ (**24**)	$PhCH=CHCH_2OCOiPr$ (**24c**)	15	80
C_6H_5-NH_2 (**41**)	C_6H_5-NHCOiPr (**41c**)	05	94
$CH_3(CH_2)_{10}CH_2SH$ (**46**)	$CH_3(CH_2)_{10}CH_2SCOiPr$ (**46c**)	60	78[c]
4-OH-C_6H_4-CH_2CH_2OH (**48**)	4-OH-C_6H_4-$CH_2CH_2OCOiPr$ (**48c**)	10	95

[a] Reactions were monitored by TLC. [b] Isolated yield. [c]CH_3CN was used as the solvent

Table 9. Pivaloylation[a] of alcohols and amines with $(t\text{-}BuCO)_2O$ catalyzed by EDPBT

Substrate	Product	Time/ min	Yield (%)[b]
CH_3-$(CH_2)_8CH_2OH$ (**1**)	CH_3-$(CH_2)_8CH_2OCOt\text{-}Bu$ (**1d**)	60	86
Ph-$(CH_2)_2CH_2OH$ (**3**)	Ph-$(CH_2)_2CH_2OCOt\text{-}Bu$ (**3d**)	60	90
Ph-$CH(CH_3)OH$ (**16**)	Ph-$CH(CH_3)OCOt\text{-}Bu$ (**16d**)	90	80
$PhCH=CHCH_2OH$ (**24**)	$PhCH=CHCH_2OCOt\text{-}Bu$ (**24d**)	90	89
C_6H_5-CH_2-NH_2 (**39**)	$C_6H_5CH_2$-NHCOt-Bu (**39d**)	15	88
4-OH-C_6H_4-CH_2CH_2OH (**48**)	4-OH-C_6H_4-$CH_2CH_2OCOt\text{-}Bu$ (**48d**)	80	82

[a] Reactions were monitored by TLC. [b] Isolated yield

Benzoic anhydride, an aromatic anhydride reacted with alcohols, amines, and thiol to give corresponding benzoates (**1e**, **3e**, **24e**, **41e**, **46e**, **48e** and **49e**). The reaction of benzoic anhydride with various alcohols, amine and thiol is summarized in Table 10. In general, the more hindered the anhydride; the slower is the acylation rate. Notably, under the present reaction condition there is not much difference in the acylation rates of alcohols, amines and thiols with acetic, propionic and isobutyric anhydride but the reaction is slower for pivalic and benzoic anhydride. This observation is consistent with the observations made by others.[21a,b]

Table 10. Benzoylation[a] of alcohols, thiol and amines with Bz_2O catalyzed by EDPBT

Substrate	Product	Time / h	Yield (%)[b]
CH_3-$(CH_2)_8CH_2OH$ (**1**)	CH_3-$(CH_2)_8CH_2OCOC_6H_5$ (**1e**)	5	75
Ph-$(CH_2)_2CH_2OH$ (**3**)	Ph-$(CH_2)_2CH_2OCOC_6H_5$ (**3e**)	2.5	87
PhCH=$CHCH_2OH$ (**24**)	PhCH=$CHCH_2OCOC_6H_5$ (**24e**)	5	85
C_6H_5-NH_2 (**41**)	C_6H_5-$NHCOC_6H_5$ (**41e**)	0.25	93
$CH_3(CH_2)_{10}CH_2SH$ (**46**)	$CH_3(CH_2)_{10}CH_2SCOC_6H_5$ (**46e**)	5	68[c]
4-OH-C_6H_4-CH_2CH_2OH (**48**)	4-OH-C_6H_4-$CH_2CH_2OCOC_6H_5$ (**48e**)	2	80
4-OH-C_6H_4-NH_2 (**49**)	4-OH-C_6H_4-$NHCOC_6H_5$ (**49e**)	0.25	92

[a] Reactions were monitored by TLC. [b] Isolated yield. [c] CH_3CN was used as the solvent.

Conclusions

The reagent EDPBT serves as an excellent source of anhydrous HBr in acetone, which catalyzes acylation of structurally diverse alcohols, amines, thiols, and phenols with different anhydrides. No bromination was observed for substrates susceptible to bromination due to consumption of active bromine in EDPBT by acetone giving bromoacetone and HBr. Solvent and steric factors in substrate as well as anhydride play a significant role during the formation of acylates. Chemoselective acylation of symmetrical diols, primary hydroxyl over secondary and phenolic, and amines over phenols has been achieved. Compared to the existing methods, which uses various acidic and basic catalysts, this method is very general, simple, gives high yield, has shorter reaction time, and is environmental friendly. In terms of compatibility and selectivity this method is superior to many of the reported methods. Due to the mild reaction conditions a number of functional groups remain intact, in spite of being capable of reacting with tribromides. The reagent EDPBT being devoid of phase transfer property and owing to the high solubility of its precursor 1,1′-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB) in water, isolation of pure acylated product can be achieved only by an aqueous work-up circumventing the need of chromatographic purification. Further, the superiority of the process lies in the recyclability of the reagent. The extensive waste of EDPBT reagent is avoided by regeneration of the reagent from the aqueous layer. It can be used without any loss of its activity for further transformations which is of significant interest.

Experimental Section

General Procedures. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was

used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetra methyl silane as the internal standard for ^{1}H NMR (300 and 400 MHz) and $CDCl_3$ or DMSO-d_6 solvents as internal standard for ^{13}C NMR (100 MHz). IR spectra were recorded in KBr or neat. GC-MS were recorded using a capillary column (30 X 0.25 mm X 0.25 mμ) in EI mode. The following acylates derived from the parent alcohols, amines and phenols by reacting with different anhydrides have been reported in the literature: acetates **1a**,[23a,b] **2a**,[8f] **3a**, [19a,20a,42a,b] **4-5a**,[21e] **7-8a**,[8f] **9a**,[21d] **10a**,[20b] **11a**,[8f] **12a**,[15b] **14a**,[21e] **15a**,[21b,42b] **16a**,[20a,21b,23b]**17a**,[8f] **19a**,[52d] **19a**,[20a,8f] **21a**,[18k] **21'a**,[51e] **22a**,[18j] **23a**,[20,21b] **24a**,[20a,21e,23b,42a-b,43] **25a**,[8f] **27a**,[18e,20a] **28a**,[52a] **29a**,[52e,8f] **30a**,[8f] **31a**,[52] **32a**,[21e] **33a**,[49] **34-36a**,[21e] **37a**,[32a] **38-44a**,[50a] **45a**,[52c] **46a**,[18j] **47a**,[42b] **47'a**,[15a] **48a**,[51d] **49a**,[50a] propionates: **1b**,[8f] **3b**,[8f] **16b**,[8f] **24b**,[8f] **41b**,[50a] **48b**,[8f] **49b**,[50a] isobutyrate: **1c**,[8f] **3c**,[8f] **16c**,[8f] **41c**,[52f] **48c**,[8f] pivalates: **1d**,[8f] **3d**,[8f] **16d**,[8f,21b] **24d**,[43] **39d**;[43] **48d**,[8f] benzoates: **1e**,[52b,] **3e**,[42a,] **24e**,[43, 21e] **41e**,[50a] **49e**.[50a]

General procedure for reaction of alcohols, amines, and phenols with acetic, propionic, isobutyric, and pivalic anhydride. Reagent EDPBT (0.25 mmol, 166.5 mg) was added to a stirred solution of acetone (10 mL) followed by 3-phenyl propanol **3** (688 μL, 5 mmol) and acetic anhydride (590 μL, 6.25 mmol). The progress of reaction was monitored by TLC. After completion of the reaction, solvent was evaporated in a rotary evaporator and admixed with ethyl acetate (25 mL). Organic layer was washed successively with water (2 x 5 mL) followed by saturated $NaHCO_3$ solution (5 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and solvent was concentrated in a rotary evaporator. The compound was sufficiently pure but for analytical data it was purified by passing it over a short column of silica gel, using a mixture of hexane and ethyl acetate as eluent to yield 855 mg (95%) of acetylated product **3a**. The aqueous layer containing EDPDB was retained for the regeneration of EDPBT.[9]

General procedure for benzoylation of alcohols, amines and phenols with benzoic anhydride. Similar to the acetylation with acetic anhydride except 5 mmol of benzoic anhydride was used per 5 mmol of the substrate.

General procedure for the reaction of thiol with acetic, propionic, and isobutyric anhydride. Similar to the reaction of alcohols with anhydrides, but acetonitrile was used instead of acetone as the reaction medium.

General procedure for benzoylation of thiols with benzoic anhydride. Similar to the acetylation with acetic anhydride but 5 mmol of benzoic anhydride was used per 5 mmol of the substrate in acetonitrile.

General procedure for selective monoacetylation of diols. Similar to the acetylation of alcohols with acetic anhydride except 6 mmol of acetic anhydride was used per 5 mmol of the substrate with lot wise addition of anhydride over a period of 30 minutes. The products were purified over a column of silica gel, using a mixture of hexane and ethyl acetate as eluent.

Regeneration of 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). To the aqueous layer originating from the above reaction containing 1,1′-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB) (1 equiv) and approximately 0.66 equiv of bromide ion (some of the bromine being consumed by the bromination of acetone) was concentrated to 5 mL, extracted

with ethylacetate (10 mL) to get rid of organic contaminants. To the aqueous layer was added KBr (354mg, 3 equiv) followed by pinchwise addition of Oxone® (1.228g, 2 equiv) under stirring. The precipitated orange solid was filtered to yield 1.17g (88%) of the bis-tribromide. The recovered reagent is identical in all respect to the parent EDPBT reagent.

In principle aqueous layers of several reactions were combined and kept for several days to allow the water to evaporate and proportionate amounts of KBr and Oxone® were added to regenerate the reagent.

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53. **Spectroscopic data of compounds, 6a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 5.26 (s, 2H), 7.56 (d, 1H, J = 8.8 Hz), 8.13 (dd, 1H, J_1= 8.4 Hz, J_2 = 2.8 Hz), 8.29 (d, 1H, J = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 62.8, 124.1, 124.2, 130.6, 135.9, 139.9, 146.8, 170.4; Mass (*m/z*) 229. **13a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 12H), 4.12 (s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 41.9, 62.6, 170.5; Mass (*m/z*) 304. **13'a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 6H), 2.06 (s, 6H), 3.74 (s, 4H), 4.10 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 23.9, 37.4, 62.2, 63.5, 98.8, 170.8; Mass (*m/z*) 260. **13"a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 12H), 3.72 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 33.0, 64.4, 98.8; Mass (*m/z*) 216; Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found C, 61.25; H, 9.26. **18a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, 3H, J = 6.6 Hz), 2.06 (s, 3H), 5.83 (q, 1H, J = 6.6 Hz), 7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 22.1, 71.5, 127.5, 128.6, 133.5, 140.2, 170.2; Mass (*m/z*) 198; Anal. Calcd for $C_{10}H_{11}ClO_2$: C, 60.46; H, 16.11. Found C, 60.58; H, 15.95. **20a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 6.74 (s, 1H), 7.24 (t, 2H, J = 7.5 Hz), 7.35 (t, 2H, J = 7.3 Hz), 7.50 (d, 2H, J = 7.5 Hz), 7.60 (d, 2H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 75.0, 119.9, 125.8, 127.7, 129.4, 140.9, 141.9, 171.7; Mass

(*m/z*) 224; Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found C, 80.59; H, 5.21. **26a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.43 (s, 9H), 2.10 (s, 3H), 3.61 (q, 2H, J = 11.2 Hz), 4.21 (m, 2H), 3.57 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.3, 28.7, 56.5, 66.6, 67.2, 80.4, 155.8, 171.3; Mass (*m/z*) 247. **46b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.17 (t, 3H, J = 7.6 Hz), 1.25 (brs, 18H), 1.58 (m, 2H), 2.56 (q, 2H, J = 7.6 Hz), 2.86 (t, 2H, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 14.6, 23.1, 29.2, 29.3, 29.5, 29.8, 29.9, 30.0, 30.02, 30.05, 32.3, 37.8; Mass (*m/z*) 258; Anal. Calcd for $C_{15}H_{30}OS$: C, 69.71; H, 11.70; S,12.41. Found C, 69.88; H, 11.62; S, 12.13. **24c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, 6H, J = 7.2 Hz), 2.60 (m, 1H), 4.73 (dd, 2H, J_1 = 6.4 Hz, J_2 = 1.6 Hz), 6.29 (m, 1H), 6.65 (d, 1H, J = 16 Hz), 7.25 (m, 1H), 7.33 (m, 2H), 7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 34.5, 65.2, 123.6, 126.8, 128.2, 128.8, 134.1, 136.4, 177.0; Mass (*m/z*) 204; Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found C, 76.58; H, 7.78. **46c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.18 (d, 6H, J = 7.2Hz), 1.26 (brs, 18H), 1.55 (m, 2H), 2.72 (septet, 1H, J = 7.2 Hz), 2.84 (t, 2H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 19.8, 23.1, 28.9, 29.3, 29.5, 29.8, 29.9, 30.0, 30.1, 32.3, 43.5, 204.3; Mass (*m/z*) 272; Anal. Calcd for $C_{16}H_{32}OS$: C, 70.53; H, 11.84; S,11.77. Found C, 71.03; H, 11.69; S, 11.69. **46e:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz), 1.26 (s, 18H), 1.67 (m, 2H), 3.06 (t, 2H, J = 7.6 Hz), 7.44 (t, 2H, J = 7.6 Hz), 7.54 (t, 1H, J = 8.0 Hz), 7.96 (d, 2H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.8, 29.0, 29.2, 29.3, 29.4, 29.60, 29.66, 29.72, 32.0, 127.0, 128.4, 133.0, 137.1, 191.8; Mass (*m/z*) 306; Anal. Calcd for $C_{19}H_{30}OS$: C, 74.45; H, 9.87; S,10.46. Found C, 73.98; H, 9.93; S, 10.22. **48e:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (t, 2H, J = 6.8 Hz), 4.48 (t, 2H, J = 6.8 Hz), 5.00 (brs, 1H), 6.78 (d, 2H, J = 8.0 Hz), 7.14 (d, 2H, J = 8.0 Hz), 7.42 (t, 2H, J = 7.6 Hz), 7.55 (m, 1H), 8.00 (d, 2H, J = 7.6 Hz). ^{13}C NMR (100 MHz $CDCl_3$) δ 34.7, 66.2, 115.6, 128.6, 129.8, 129.9, 130.2, 130.3, 133.2, 154.6, 166.9. Mass (*m/z*) 242.