JOC Article

Easily Prepared Azopyridines As Potent and Recyclable Reagents for Facile Esterification Reactions. An Efficient Modified Mitsunobu Reaction

Nasser Iranpoor,* Habib Firouzabadi,* Dariush Khalili, and Somayeh Motevalli

Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran

iranpoor@chem.susc.ac.ir; firouzabadi@chem.susc.ac.ir

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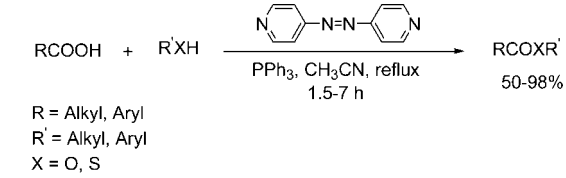

The 2,2′-, 3,3′-, and 4,4′-azopyridines (azpy) and their alkyl pyridinium ionic liquids were studied as a new class of electron-deficient reagents for Mitsunobu esterification reactions. Among these compounds, 4,4′-azopyridine was found to be the most suitable one for esterification and thioesterification reactions. This new reagent promises to provide general and complementary solutions for separation problems in Mitsunobu reactions without restricting the reaction scope and facilitates the isolation of its hydrazine byproduct. The pyridine hydrazine byproduct can be simply recycled to its azopyridine by an oxidation reaction.

Introduction

Esterification reactions are well recognized as fundamental processes in various fields of organic synthesis.[1,2] It has a long history in both laboratory work and industrial processes on account of its versatility. Over the past decade, different catalysts have been proposed as alternatives to the Brønsted acids for direct condensation of carboxylic acids with alcohols.[3] Apart from esterification methods based on Lewis acid catalyses, Mitsunobu reaction is a well-established fundamental reaction and has been applied widely in organic synthesis.[4] In this reaction, a unique dehydration occurs between alcohols and various Brønsted−Lowry acids utilizing a combination of diethyl azodicarboxylate (DEAD)−triphenylphosphine (TPP).

Without any prerequisite activation of the alcohol, this redox condensation reaction proceeds under mild conditions with complete inversion of stereochemistry.[5] In the traditional Mitsunobu reaction using DEAD and TPP, one major problem that has somewhat hampered the reaction is the laborious purification of the product from dihydro-DEAD because of its moderate polarity and half-crystalline nature.[6] Thus, recently, numerous modified reagents and separation techniques have been developed with the aim of facilitating isolation of the desired product from the reaction mixture.[7] For example, it has been demonstrated that 2-(trimethylsilyl)ethyl 4-(diphenylphosphanyl)benzoate and diisopropyl azodicarboxylate (DIAD) are also efficient reagents that facilitate product isolation.[8] Di-*p*-chlorobenzyl azodicarboxylate (DCAD) as an alternative reagent to DEAD has been also used as a useful reagent in Mitsunobu reaction.[9]

Results and Discussion

DEAD is explosive, photosensitive, toxic, shock sensitive, thermally unstable, and no longer is produced.[10] In order to

* To whom correspondence should be addressed. Phone: +98 711 2284822. Fax: +98 711 2280926.

(1) Otera, J.; *Esterification Methods, Reactions and Applications*; Wiley-VCH: Weinheim, Germany, 2003.

(2) (a) Franklin, A. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2451–2465. (b) Franklin, A. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3537–3554.

(3) (a) Fernandes, M. L. M.; Bolzani Saad, E.; Meira, J. A.; Ramos, L. P.; Mitchell, D. A.; Krieger, N. *J. Mol. Catal B* **2007**, *44*, 8–13. (b) Liu, Y.; Lotero, E.; Goodwin, J. G., Jr. *J. Catal.* **2006**, *243*, 221–228. (c) Barbosa, S. L.; Dabdoub, M. J.; Hurtado, G. R.; Klein, S. I.; Baroni, A. C. M.; Cunha, C. *Appl. Catal. A* **2006**, *313*, 146–150. (d) Pan, W. B.; Chang, F. R.; Wei, L. M.; Wu, M. J.; Wu, Y. C. *Tetrahedron Lett.* **2003**, *44*, 331–334. (e) Mohammed Khan, K.; Maharvi, G. M.; Hayat, S.; Ullah, Z.; Choudhary, M. L.; Rahman, A. *Tetrahedron* **2003**, *59*, 5549–5554. (f) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Tetrahedron Lett.* **2002**, *43*, 879–882.

(4) (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656. (c) Hughes, D. L. *Org. Prep. Proceed. Int.* **1996**, *28*, 127–164 .

(5) (a) Shi, Y. J.; Hughes, D. L.; McNamara, J. M. *Tetrahedron Lett.* **2003**, *44*, 3609–3611. (b) Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 3417–3420.

(6) Tsunoda, T.; Kaku, H.; Itô, S. *TCI Mail No. 123,* 2005.

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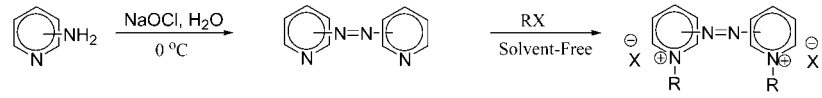
SCHEME 1



1a: 4-aminopyridine
1b: 2-aminopyridine
1c: 3-aminopyridine

2a-c: 4,4'; 2,2'; 3,3' isomers

For 4,4':
3a: R = *n*-butyl, X = Br
3b: R =CH_3, X = CH_3SO_4
3c: R = *n*-butyl, X = PF_6
3d: R = *n*-octyl, X = PF_6
3e: R = *n*-butyl, X = NTf_2
For 3,3':
3f: R = *n*-butyl, X = Br
3g: R = *n*-butyl, X = PF_6

reduce these problems, and along with our continued interest mainly on the modification of Mitsunobu reaction in our laboratory,[11] we studied the possibility of using azopyridines (**2a**−**c**) and their pyridinium salts ionic liquids (ILs) (**3a**−**g**) (Scheme 1) as a new class of reagents for Mitsunobu esterification reactions.

In this paper, we have presented the application of azopyridines (**2a**−**c**) and also their pyrdinium salts ionic liquids (**3a**−**g**) as new alternatives for diethyl azodicarboxylate (DEAD) to perform the Mitsunobu esterification reactions.

Azopyridines (**2a**−**c**) were simply prepared according to the literature procedure by oxidation of their corresponding aminopyridines with sodium hypochlorite at 0 °C.[12] These azo compounds were then converted to their methyl, *n*-butyl, and *n*-octyl pyridinium salts having Br^-, PF_6^-, $CH_3SO_4^-$, and NTf_2^- as counterions (Scheme 1). Azopyridines (**2a**−**c**) were then used as reagent (1.2−1.3 equimolar) in conjunction with PPh_3 (1.2−1.3 equimolar) for the esterification of 4-nitrobenzoic acid with benzyl alcohol in refluxing acetonitrile. The results are tabulated in Table 1. However, their pyridinium salts (**3a**−**g**) which are liquid upon heating to 80−90 °C were used either as reagent in refluxing acetonitrile or as an ionic liquid media and reagent for esterification of 4-nitrobenzoic acid.

Our studies showed that 2- and 4-azopyridines are nearly equally efficient reagents and are more reactive than their 3-isomer for esterification of 4-nitrobenzoic acid with benzyl alcohol (Table 1, entries 1−3). This can be explained on the basis of the stabilization of the produced negative charge after

TABLE 1. Esterification of 4-Nitrobenzoic Acid with Benzyl Alcohol in the Presence of PPh_3 and Azo Compounds (2a−c, 3a−g) under Different Reaction Conditions

Entry	Azo compound (molar equiv)	PPh_3 (molar equiv)	Reaction Time (h)	Yield % of Benzyl-4-nitrobenzoate
1[a]	**2a** (1.2)	1.2	2	93
2[a]	**2b** (1.2)	1.2	2	90
3[a]	**2c** (1.3)	1.3	3	50
4[a]	**3a** (1.3)	1.3	6	50
5[a]	**3b** (1.3)	1.3	6	6
6[a]	**3c** (1.3)	1.3	6	50
7[a]	**3d** (1.3)	1.3	6	52
8[b]	**3e** (3)	3	6	65
9[a]	**3f** (1.2)	1.2	6	20
10[a]	**3g** (1.2)	1.2	6	20

[a] The reaction was performed in refluxing acetonitrile. [b] The ionic liquid azo compound was used as solvent of the reaction at 80−90 °C.

reaction with PPh_3 through the resonance effect of the nitrogen atom in the 2- and 4-positions of azpys (**2a**,**b**) (Scheme 2, **I**). The lower reactivity of the pyridinium salts of azpys (**3a**−**g**) compared to that of the azo pyridines (**2a**−**c**) in the esterification of 4-nitrobenzoic acid with benzyl alcohol (Table 1, entries 4−10) again can be rationalized by electronic effects. In the pyridinium salts of azopyridines, the electrophilicity of azo groups is increased for the reaction with PPh_3 due to the presence of positive charge on the ring's nitrogen. However, the negative charge which is produced by the addition of PPh_3 to the azo group (Scheme 2, **III**) is greatly dispersed by the positive charge on the nitrogen in 4- and 2-positions of the pyridinium ring. This causes severe reduction of the basicity of adduct **III** obtained from the reaction of PPh_3 and the azo functionality of the pyridinium salts and seriously decreases their reactivity compared to **I** for deprotonation of carboxylic acids which is the crucial step in the Mitsunobu esterification reaction. In support of this suggestion, our NMR study showed that azopyridine (**2a**) is not protonated by 4-nitrobenzoic acid, and therefore the lower reactivity of the alkyl pyridinium salts is attributed to the presence of the positive charge on the nitrogen atom of their aromatic ring.

Among the studied azo compounds, 2,2′- and 4,4′-azopyridine (**2a**) were found to be the most efficient and suitable alternatives for DEAD in the Mitsunobu reaction. However, since the yield of the reaction for synthesis of **2a** is much higher than for **2b**, this compound was chosen as the reagent of choice in this reaction. We therefore focused our attention toward esterification of various acids and alcohols and observed that 4,4′-azopyridine (**2a**) as an easily prepared solid azo compound is very efficient (Scheme 3) and useful for this purpose under our optimized reaction conditions. Apart from the ease of handling and preparation of **2a**, its produced hydrazine byproduct from this

(7) (a) Toy, P. H.; But, T. Y. S. *J. Am. Chem. Soc.* **2006**, *128*, 9636–9637. (b) Véliz, E. A.; Beal, P. A. *Tetrahedron Lett.* **2006**, *47*, 3153–3156. (c) Bálint, A. M.; Bodor, A.; Gömöry, Á.; Vékey, K.; Szabó, D.; Rábai, J. *J. Fluorine Chem.* **2005**, *126*, 1524–1530. (d) Szabó, D.; Bonto, A. M.; Kövesdi, I.; Gömöry, Á.; Rábai, J. *J. Fluorine Chem.* **2005**, *126*, 641–652. (e) Harned, A. M.; He, H. S.; Toy, P. H.; Flynn, D. L.; Hanson, P. R. *J. Am. Chem. Soc.* **2005**, *127*, 52–53. (f) Dandapani, S.; Curran, D. P. *Chem.—Eur. J.* **2004**, *10*, 3130–3138. (g) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772. (h) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855–3864. (i) Dobbs, A. P.; McGregor-Johnson, C. *Tetrahedron Lett.* **2002**, *43*, 2807–2810. (j) Pelletier, J. C.; Kincaid, S. *Tetrahedron Lett.* **2000**, *41*, 797–800 .

(8) Yoakim, C.; Guse, I.; O'Meara, J. A.; Thavonekham, B. *Synlett* **2003**, 473–476.

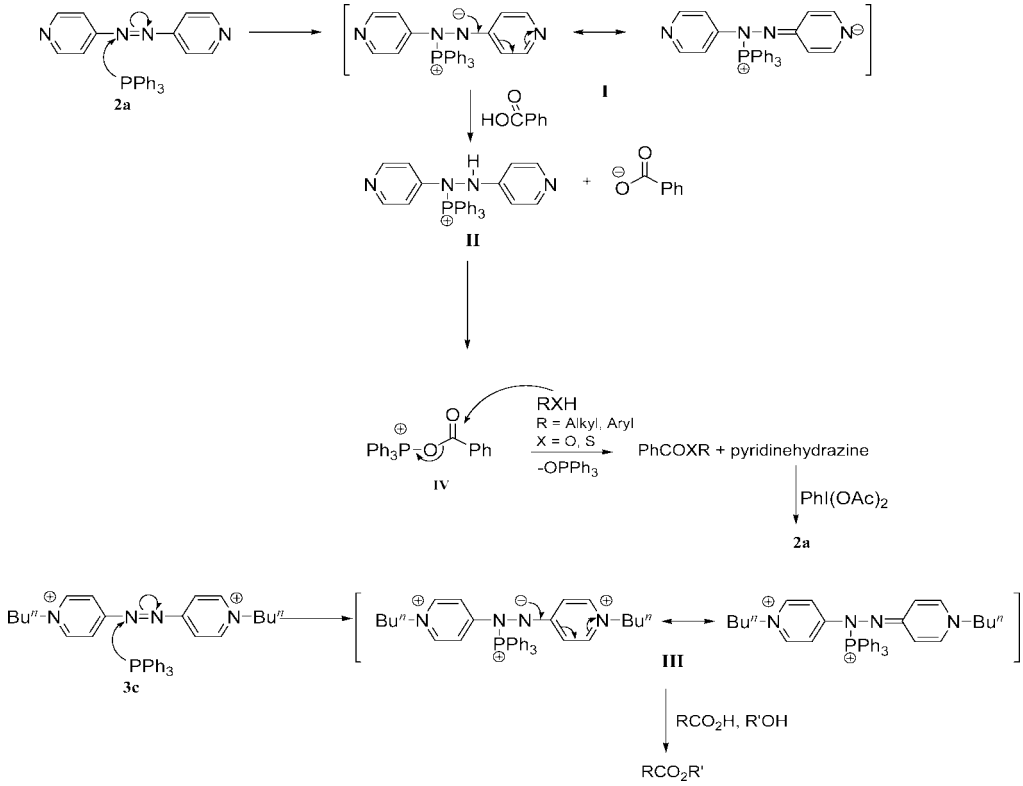
(9) Lipshutz, B. H.; Chung, D. W.; Rich, B.; Corral, R. *Org. Lett.* **2006**, *8*, 5069–5072.

(10) (a) Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, *3*, 317–334, and the reference cited therein. (b) See: http://chemistry.about.com/cs/molecules/a/blmoldead.htm.

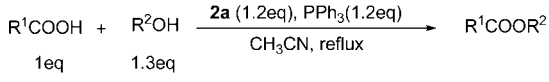
(11) (a) Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N. *Tetrahedron* **2006**, *62*, 5498–5501. (b) Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N. *Tetrahedron Lett.* **2006**, *47*, 8247–8250. (c) Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi, N. *Tetrahedron Lett.* **2004**, *45*, 3291–3294. (d) Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Azadi, R. *Synthesis* **2004**, *1*, 92–96. (e) Iranpoor, N.; Firouzabadi, H.; Aghapour, G. H.; Vaez Zadeh, A. R. *Tetrahedron* **2002**, *58*, 8689–8693.

(12) Launay, J. P.; Tourrel-Paggis, M.; Lipskier, J. F.; Marvaud, V.; Joachim, C. *Inorg. Chem.* **1991**, *30*, 1033–1038.

SCHEME 2



SCHEME 3



R^1 = Et, C_6H_5 -, *p*-NO_2-C_6H_4 -, *p*-CH_3-C_6H_4 -
R^2 = alkyl 1°, 2°

azo is precipitated during the reaction and can be easily removed from the reaction mixture. This makes the workup much easier compared to DEAD.

To optimize the reaction conditions, we first examined the effect of different ratios of RCO_2H/ROH/PPh_3/azpy in dry CH_3CN for the conversion of benzyl alcohol to benzyl-4-nitrobenzoate. Employing the ratio of 1/1.3/1.2/1.2 in refluxing CH_3CN gave the best result and produced benzyl-4-nitrobenzoate after 2 h in 93% isolated yield. With the optimized conditions in hand, we screened a representative range of structurally different alcohols for the reaction. Representative results are summarized in Table 2.

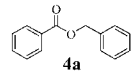
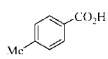
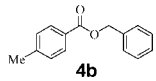
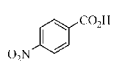
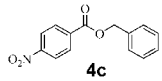
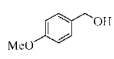
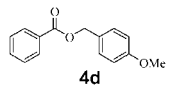
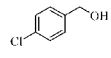
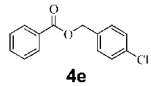
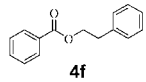
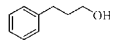
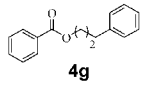
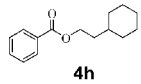
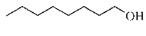
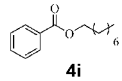
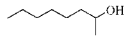
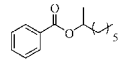
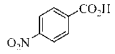
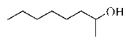
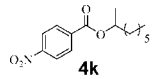
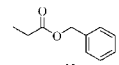
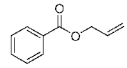
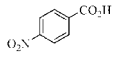
The order of addition of the reagents is similar to the classical Mitsunobu reaction. The mixture of azpy **2a** and acid is first prepared in acetonitrile, and then a solution of PPh_3 and alcohol is added to this mixture. Moreover, when this reaction was carried out in the absence of PPh_3, no reaction occurred and the staring materials remained intact.

We applied the optimized conditions to the reaction of different substituted benzoic acids with a wide range of primary and secondary alcohols to produce the desired esters in high yields (Table 2). Furthermore, the effect of various substituents on the reaction outcome was studied on a series of substituted benzoic acids. The least acidic members (H, 4-Me) provided yields of 65−86%, while the most acidic (4-NO_2) furnished yields in the 76−93% range. Consequently, electron-deficient benzoic acids gave better yields (Table 2, entries 3 and 11) with the same alcohol (benzyl alcohol for entry 1 and 2-octanol for entry 10, compare to entries 1, 2, and 10). These results are consistent with the previous studies on the effect of acid strength on Mitsunobu esterification.[13]

Our observations show that the esterification reaction also works well for benzylic alcohols substituted with OMe and Cl (Table 2, entries 4 and 5). 2-Phenyl-1-ethanol also reacted cleanly without any styrene formation (Table 2, entry 6), indicating that β-elimination does not occur. To further evaluate the influence of the steric bulk of alcohols, the reaction of 1- and 2-octanol with benzoic acid in the presence of **2a** and PPh_3 was also tested. The use of more bulky secondary alcohols as the nucleophile in this system affords lower yields in comparison with primary alcohols. These results suggested that the steric bulk was important to the yield of esterification. Propionoic acid as an aliphatic carboxylic acid was also examined as proelectrophile. In this case, the reaction afforded similar or slightly higher yield than did to the other aromatic acids (Table 2, entry 12 compared to entries 1 and 2). The yields reported in Table 2 pertain to the isolated mass of the purified esters obtained by silica gel chromatography. The stereochemical inference of the reaction was then probed utilizing L-menthol as the chiral alcohol. Menthol reacted with both 4-nitrobenzoic acid and benzoic acid in refluxing acetonitrile to give the corresponding chiral menthol esters in good yields (Table 2, entries 14 and 15). According to the specific ^{1}H NMR data reported in the literature for both D- and L-menthyl 4-nitrophenylbenzoate and

(13) (a) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967–2971. (b) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234–236. (c) Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317–4320. (d) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017–3020.

TABLE 2. Esterification Reactions Promoted by azpy 2a[a]

Entry	Acid	Alcohol	Product [b]	Time(h)	Yield%
1			 **4a**	3	86
2			 **4b**	6	69
3			 **4c**	2	93
4			 **4d**	4	89
5			 **4e**	3.5	82
6			 **4f**	4	85
7			 **4g**	4	80
8			 **4h**	4.5	70
9			 **4i**	3	79
10			 **4j**	6	65
11			 **4k**	3	76
12			 **4l**	3	88
13			 **4m**	3	90
14			**4n**	5	75
15			**4o**	8	70

[a] The stoichiometric ratio of the reactants for $RCO_2H/ROH/PPh_3$/azpy in refluxing CH_3CN is 1/1.3/1.2/1.2. [b] The products were identified by their spectral data.

menthyl benzoate,[14] the stereochemistry of the reaction under our conditions is found to be with perfect retention of configuration. The observed retention of configuration is thought to arise through the direct attack of the alcohol at the carbonyl carbon atom of the intermediate acyloxyphosphonium salt **IV** shown in Scheme 2. This is in accordance with those methods which occur with retention of configuration.[15] According to this hypothesis, an initial acyloxyphosphonium ion **IV** is generated by the attack of the more nucleophilic carboxylate anion rather than the alcohol at the phosphorus center (Scheme 2).

SCHEME 4

Although the reaction times with DEAD are relatively shorter than using **2a**, the reaction yields are comparable. A clear advantage gained using the easily prepared solid and 4,4′-azopyridine is that the side product 4,4′-bispyridyl hydrazine can be largely removed by filtration, thereby simplifying the purification process. This hydrazine byproduct can be simply recycled to its azo compound **2a** by its oxidation with iodosobenzene diacetate in DMSO at room temperature for 6 h.

Since thioesters are among the most used protecting groups for thiols,[16] especially to protect phosphate groups in nucleotide synthesis,[17] we were especially interested in broadening the scope of our new azo reagent **2a** for the synthesis of thioesters. The syntheses of thioesters from the reaction of carboxylic acids and thiols were performed successfully using **2a** under similar reaction conditions as used for alcohols (Scheme 4).

We found that molar ratios of 1/1.3/1.1/1.1 for RCO_2H/RSH/azpy/Ph_3P gave the best yields of the desired thioesters. The order of addition is similar to that carried out for alcohols. We then applied this optimized conditions to the conversion of different carboxylic acids and thiols into their corresponding thioesters. The obtained results are shown in Table 3.

Factors such as electron deficiency of carboxylic acid and thiol and the steric bulk of thiols have profound effect on the yield of reaction. Inspection of Table 3 reveals that primary thiols (Table 3, entries 1−6 and 11) all afford good yields of the desired thioesters. Furfuryl mercaptan (Table 3, entry 7) gave poor yield of the corresponding thioester due to its lower reactivity. Further examination of the presented data of Table 3 reveals a distinct trend in which the use of stronger aryl acids, such as 4-nitrobenzoic acids, results in higher yields of the product (84−95%, entries 3, 5, and 10) compared to weaker acids such as benzoic and 4-methylbenzoic acids (70−89%, entries 1, 2, 4, and 6−9).

Another promising feature of this new azo reagent 4,4′-azopyridine **2a** in Mitsunobu reaction is the efficient preparation of esters of phenol derivatives from carboxylic acids and phenols upon treatment with **2a** and triphenylphosphine. To the best of our knowledge, there are very few reports concerning the use of the Mitsunobu reaction within the context of coupling benzoic

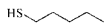
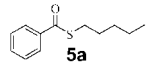
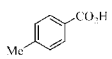
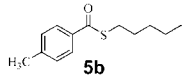
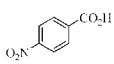
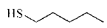
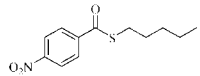
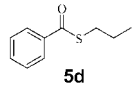
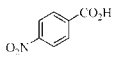
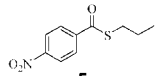
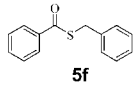
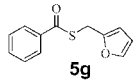
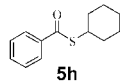
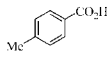
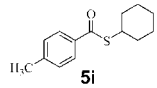
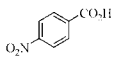
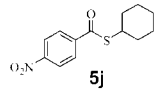
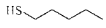
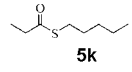
(14) (a) McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *J. Org. Chem.* **2003**, *68*, 1597–1600. (b) Silverman, R. B.; Forrester, M. T.; Gomez-Vidal, J. A. *Org. Lett.* **2001**, *3*, 2477–2479.

(15) (a) Dinsmore, C. J.; Mercer, S. P. *Org. Lett.* **2004**, *6*, 2885–2888. (b) Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648–1652. (c) Smith, A. B., III.; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102–11113. (d) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751–1753. (e) Ahn, C.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1754–1759. (f) McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *Angew.Chem., Int. Ed.* **2003**, *42*, 4051–4054. (g) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049–3054.

(16) (a) Cavelier, F.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1990**, *127*, 210–225. (b) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, *16*, 2643–2646.

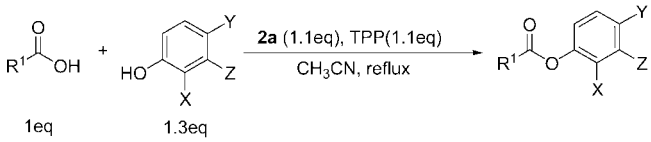
(17) Agarwal, K. L.; Fridkin, M.; Jay, E.; Khorana, H. G. *J. Am. Chem. Soc.* **1973**, *95*, 2020–2021.

TABLE 3. Synthesis of Thioesters under Conditions of the Mitsunobu Reaction Using azpy 2a[a]

Entry	Acid	Thiol	Product[b]	Time(h)	Yield %
1			 **5a**	3	85
2			 **5b**	6	77
3			 **5c**	2	95
4			 **5d**	4	89
5			 **5e**	3.5	94
6			 **5f**	4	83
7			 **5g**	4	64
8			 **5h**	4.5	77
9			 **5i**	3	70
10			 **5j**	6	84
11			 **5k**	3	86

[a] The molar ratio of the reactants for RCO_2H/RSH/PPh_3/azpy in refluxing CH_3CN is 1/1.3/1.1/1.1. [b] The products were identified by their spectral data.

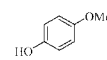
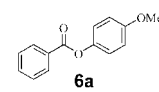
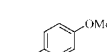
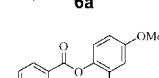
SCHEME 5



acids with phenolic nucleophiles.[18] While phenols have been previously employed in coupling reactions with other functional groups,[19] there was an account of the reactivity or overall effectiveness of this process utilizing benzoic acids as starting materials.[18] In view of these facts, and to disseminate the usages of 4,4′-azopyridine (**2a**), we focused our attention on the synthesis of phenolic esters. The condensation reaction between carboxylic acids with *ortho*- and *para*-substituted phenols was carried out in refluxing acetonitrile to afford the desired products (Scheme 5).

The optimized stoichiometric ratio of R^1CO_2H/phenols/azpy/Ph_3P for the conversion of phenols to phenyl benzoate was found to be 1/1.3/1.1/1.1. The order of addition in this case is the same as that used for alcohols and thiols. We thereafter used the optimized conditions for the synthesis of phenolic esters. Table 4 lists the successful results of the esterification between various

TABLE 4. Preparation of Phenyl Esters via Mitsunobu Reaction Using azpy 2a[a]

Entry	Acid	Phenol	Product[b]	Time(h)	Yield %
1			 **6a**	3	92
2			 **6b**	7	50
3			**6c**	1.5	97
4			**6d**	3	96
5			**6e**	3	93
6			**6f**	3	93
7			**6g**	3.5	98
8			**6h**	4	92
9			**6i**	5	85
10			**6j**	5	83
11			**6k**	5	81
12			**6l**	2	97

[a] The stoichiometric ratio of the reactants for RCO_2H/ArOH/PPh_3/azpy in refluxing CH_3CN is 1/1.3/1.1/1.1. [b] The products were identified by their spectral data.

(18) (a) Fitzjarrald, V. P.; Pongdee, R. *Tetrahedron Lett.* **2007**, *48*, 3553–3557. (b) Yu, Y.; Maeda, T.; Mamiya, J.; Ikeda, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 881–883. (c) Heasley, B. H.; Jarosz, R.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2735–2740.

carboxylic acids with different substituents on the phenolic component using 4,4′-azopyridine (**2a**). As outlined in Table 4, we tried to determine the effects of incorporating various functional groups as well as differing substitution patterns on the phenol component.

The reaction of benzoic acid with electron-rich phenols (Table 4, entries 1, 3−9, and 12) was successful and gave the desired esters in good to excellent yields. On the other hand, the presence of electron-withdrawing groups in phenol decreases the overall yield of reaction (Table, entries 10 and 11). It is also apparent that varieties of electron-donating substituents on the phenol provide synthetically useful yields. As the steric hindrance around the reacting nucleophilic oxygen atom on the phenol increases, we observed a slight decrease in the overall efficiency of the process with *ortho*-substituted phenols (Table 4, entries 4, 6, and 11). Especially remarkable is the reaction of benzoic acid with 2-*tert*-butyl-4-methoxyphenol that gave the desired ester in moderate yield (Table 4, entry 2). This method is also applicable to the reaction of carboxylic acids and alcohols with amines, which is under investigation.

In conclusion, the use of 4,4′-azopyridine (azpy) (**2a**) as a new alternative to DEAD in conjunction with PPh_3 offers a simple, novel, and convenient method for the conversion of wide varieties of alcohols, thiols, and phenols to their corresponding esters. The ease of preparation and handling, ease of separation of its pyridine hydrazine, and its recyclability and good to high yields of the desired esters can be considered as other strong points of using this reagent in Mitsunobu reactions.

Experimental Section

General procedures for the preparation of *N*,*N*′-dialkylazopyridinium salts and esters of alcohols, thiols, and phenols are as follows. The procedures for synthesis of azopyridines, oxidation of pyridine hydrazine, and spectral data for the products are included in the Supporting Information.

General Procedure for the Synthesis of *N*,*N*′-Dialkylazopyridinium Bromide. Azopyridine (1.0 mmol) and 5.0 mmol of *n*-alkylbromide were placed in a round-bottom flask fitted with a reflux condenser and stirred at 80 °C for 20 h. The resulting solid was allowed to cool to room temperature and then was washed with 5 × 5 mL of diethyl ether. *N*,*N*′-Dialkylazopyridinium bromide was obtained in quantitative yield and was used without further purification.

General Procedure for the Synthesis of *N*,*N*′-Dialkylazopyridinium Hexafluorophosphate. To prepare hexafluorophosphoric acid salt, an aqueous solution of NH_4PF_6 (3.0 mmol) was slowly added to the aqueous solution of azopyridinium bromide (1 mmol). After stirring for 10 h at room temperature, the PF_6 salt was accommodated at the bottom of the flask. It was filtered and washed several times with water to remove the excess of NH_4PF_6. Finally, upon drying under vacuum at 60 °C, *N*,*N*′-dialkylazopyridinium hexafluorophosphate was obtained as a colored solid.

General Procedure for the Synthesis of Esters from Alcohols. To a flask containing a stirred mixture of 4,4′-azopyridine (0.216 g, 1.2 mmol) and acid (1 mmol) in dry CH_3CN (3 mL) was added a solution of PPh_3 (0.312 g, 1.2 mmol) and alcohol (1.3 mmol) in acetonitrile. The reaction mixture was refluxed for several hours and monitored by TLC. After completion of the reaction as monitored by TLC, the reaction mixture was filtered to remove the produced pyridine hydrazine and then concentrated on a rotary evaporator to give a viscous oil. The crude product was purified by short column chromatography on silica gel. The product obtained was characterized by routine spectroscopic methods.

General Procedure for the Synthesis of Esters from Thiols. To a stirred mixture of 4,4′-azopyridine (1.2 mmol, 0.216 g) and acid (1 mmol) in dry CH_3CN (3 mL) was added a solution of PPh_3 (0.312 g, 1.2 mmol) and thiol (1.3 mmol) in acetonitrile. The reaction mixture was refluxed for several hours. After completion of the reaction, the produced pyridine hydrazine was filtered and the solution was concentrated on a rotary evaporator to give a viscous oil. After purification using a short column of silica gel, the product was obtained.

General Procedure for the Synthesis of Esters from Phenols. To a flask containing a stirring mixture of 4,4′-azopyridine (0.20 g, 1.1 mmol) and acid (1 mmol) in dry CH_3CN (3 mL) was added a solution of PPh_3 (0.286 g, 1.1 mmol) and phenol (1.3 mmol) in acetonitrile. The reaction mixture was refluxed until TLC indicated complete consumption of the benzoic acid. The reaction mixture was filtered to remove pyridine hydrazine and then concentrated on a rotary evaporator to give a viscous oil. The product was purified by short column chromatography on silica gel.

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Supporting Information Available: Experimental procedures, spectroscopic data, ^{13}C and/or ^{1}H NMR spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) (a) Yamaguchi, S.; Tsuchia, N.; Miyazawa, M.; Hirai, Y. *J. Org. Chem.* **2005**, *70*, 7505–7511. (b) Chen, K. X.; Njoroge, F. G.; Pichardo, J.; Prongay, A.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan, V. *J. Med. Chem. Soc.* **2006**, *49*, 567–574. (c) Jacob, A. M.; Moody, C. J. *Tetrahedron Lett.* **2005**, *46*, 8823–8825.