Short communication

One-Pot Synthesis of Carboxylic Acid Esters in Neutral and Mild Conditions by Triphenylphosphine Dihalide [Ph_3PX_2 (X=Br, I)]

Alireza R. Sardarian,* Maryam Zandi and Soghra Motevally

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

** Corresponding author: E-mail: sardarian@susc.ac.ir;*
Tel. (711)6137710, Fax: (711)2286008

Received: 30-10-2008

Abstract

We report the preparation of aromatic and aliphatic carboxylic acid esters in the presence of triphenylphosphine dibromide or triphenylphosphine diiodide and N,N-dimethylaminopyridine in dichloromethane at room temperature in good to excellent yields.

Keywords: Esterification, triphenylphosphine dibromide, triphenylphosphine diiodide, N,N-dimethylaminopyridine, carboxylic acid

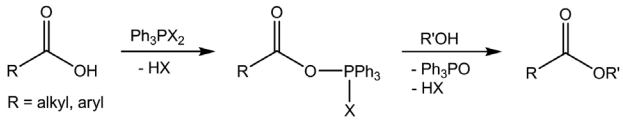
1. Introduction

The equilibrium is the biggest problem that is frequently encountered in the esterification reactions of carboxylic acids. To overcome this problem one of the reactants must be used in excess and /or one of the products must be removed during the reaction. Use of the non-equilibrium esterification reaction approach can be effective to bypass the problem with the aid of a) using an activated derivative of carboxylic acids such as acid anhydrides and halides, b) reaction of carboxylic acid with alkoxides, or c) in situ production of activated forms of carboxylic acid by electrophilic activator reagents.[1] Using electrophilic activators is a popular and attractive method for the preparation of esters, for example: carbodiimide activators,[2] DEAD/Ph_3P (Mitsunobu reaction),[3] Ph_3P/CCl_4,[4a] Ph_3PBr_2/3-trimethylsilyl-1-3-oxazolidinone,[4b] Ph_3P/NBS or NBI,[4c] Ph_3P/trichloroisocyanuric acid,[4d] Ph_3P/benzyl azide,[4e] cyanomethylene tributylphosphorane,[5] $(RO)_2POH/CCl_4$,[6] phosphonium salt ionic liquid,[7] 2-halo-1-methyl pyridinium salt,[8] CH_3SO_2Cl/Et_3N,[9a] TsCl/pyridine,[9b] Me_2NSO_2Cl/DMAP,[9c] $Ph_3PO/(FSO_2)_2O$,[10] triflic anhydride,[11] N,N-bis(2-oxo-3-oxazolidinyl)phosphordiamide chloride,[12] benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate,[13] 2,2´-bipyridyl-6-yl hexanoate/CsF,[14] 4,5-dichloro-1,2,3-dithiazolium chloride,[15] 1-hydroxybenzotriazole/trichloromethylcarbono chloridate,[16] N-hydroxysuccinimide/DCC,[17] 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-ethylmorpholinium chloride/N-methylmorpholine,[18] diiodotributylphosphorane and diiodotriphenylphosphorane/HMPTA,[19] organocatalytic Mitsunobu reactions,[20] fluorous DEAD reagent[21] and Ph_3PBr_2/K_2CO_3.[22] Methods developed so far have their own disadvantages. For example, the use of an extremely anhydrous reaction conditions, long reaction times, high reaction temperatures, expensive reagents, the use of highly toxic solvents and chemicals, tedious work-up, by-product formation and the use of large excess of reagents. Therefore, the search for development of simple, mild, and highly efficient method is still highly demanded.

We wish to introduce in this account a simple, mild and an efficient method for esterification of carboxylic acids using triphenylphosphine dibromide and triphenylphosphine diiodide.

2. Results and Discussion

Esterification of the different aliphatic and aromatic carboxylic acids was studied at room temperature by Ph_3PBr_2 and Ph_3PI_2 as a simple and cheap system (Scheme 1).



Scheme 1:

To optimize the reaction conditions, we examined the esterification of 4-nitrobenzoic acid by Ph_3PBr_2 or Ph_3PI_2 in the presence of triethylamine, pyridine, N,N-dimethylaminopyridine (DMAP), DBU and K_2CO_3 as base in dichloromethane as solvent at room temperature. The results showed that N,N-dimethylaminopyridine (DMAP) is the most suitable base (Table 1).

Table 1. Effect of base on the esterification of 4-nitrobenzoic acid with *n*-butanol at room temperature.

Base	Mole Ratio Base: Acid	Ph_3PBr_2 Time (min)	Ph_3PBr_2 Yield (%)	Ph_3PI_2 Time (min)	Ph_3PI_2 Yield (%)
Et_3N	3:1	30	80	30	70
Pyridine	3:1	30	70	15	70
DBU	3:1	30	10	30	40
DMAP	2:1	2	99	2	95
K_2CO_3	5:1	30	N.R	30	N.R

The effect of solvent was also investigated among different common solvents (THF, CH_3CN, dichloromethane, ethyl acetate, chloroform and *n*-hexane), and dichloromethane afforded the best result (Table 2).

With optimized reaction conditions in hand, we initially conduct esterification of 4-nitrobenzoic acid in the presence of PPh_3X_2 (X=Br, I) and DMAP with simple aliphatic alcohols in dichloromethane at room temperature. Results, presented in Table 3, indicated that the corresponding esters were produced in excellent yields (entries 1–5) in all cases investigated. Moreover, the esterification of *t*-butanol as a highly sterically hindered alcohol, was also achieved in excellent yields, although in a longer reaction time compared to unhindered alcohols. Phenol and its sterically hindered derivative, 2,6-dimethylphenol, also reacted with 4-nitrobenzoic acid to the corresponding esters in good yields after 15 min (entries 8, 9). Allyl alcohol was also converted to the corresponding ester in excellent yield within 2 minutes (entry 7). Based on the data collected in Table 3, *n*-butanol was selected as the most suitable alcohol for studying esterification of the other carboxylic acids.

Table 2. The effect of solvent on the esterification of 4-nitrobenzoic acid with *n*-butanol in the presence of DMAP at room temperature.

Solvent	Mole ratio DMAP:Acid	Time (min) Ph_3PBr_2	Time (min) Ph_3PI_2	Yield (%) Ph_3PBr_2	Yield (%) Ph_3PI_2
n-Hexane	2:1	720	60	40	N.R
EtOAc	2:1	720	30	N.R	50
THF	2:1	60	60	15	40
$CHCl_3$	2:1	2	2	94	85
CH_2Cl_2	2:1	2	2	99	95
CH_3CN	2:1	3	2	94	70

Esterification of benzoic acid and its derivatives with electron-releasing and electron-withdrawing groups (entries 1-7) were also investigated with *n*-butanol in the presence of both reagents and DMAP in dichloromethane at room temperature. The results were summarized in Table 4.

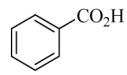
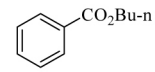
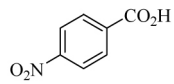
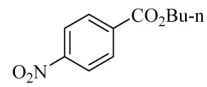
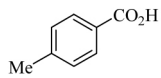
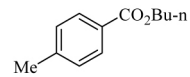
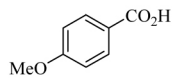
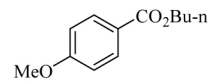
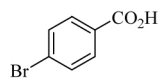
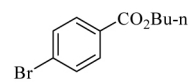
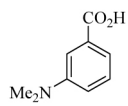
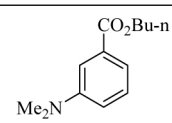
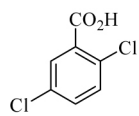
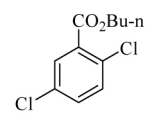
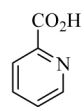
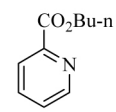
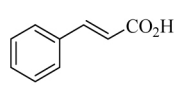
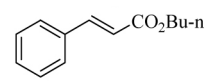
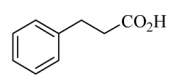
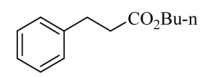
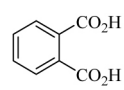
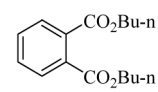
Data presented in Table 4 showed that, the rate of the esterification reaction was not sensitive to the type of substitution but to the mole ratio of DMAP:acids. This effect might be related to the pK_a of carboxylic acids, because the weaker carboxylic acids required higher amount of DMAP to be converted to the corresponding carboxylate anion which was probably necessary for attacking on PPh_3X_2 (X=Br, I).

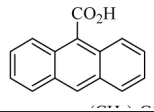
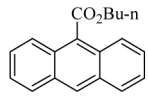
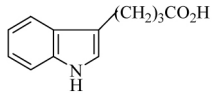
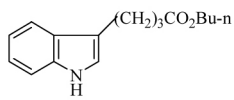
In addition, pyridine-2-carboxylic acid as a heteroaromatic carboxylic acid (entry 8, Table 4) was, at the same reaction conditions, converted to the related ester in good yield. Even anthracene-10-carboxylic acid, despite of having considerable steric hindrance, was converted to the

Table 3. Preparation of different types of esters of 4-nitrobenzoic acid by using Ph_3PBr_2 and Ph_3PI_2 as reagent and DMAP in dichloromethane at room temperature.

Entry	Alcohol	Ester	Mole ratio DMAP:Acid	Reaction Time (min)	Yield (%) Ph_3PBr_2	Yield (%) Ph_3PI_2
1	CH_3OH	Ar CO_2CH_3	2:1	2	96	95
2	CH_3CH_2OH	$ArCO_2CH_2CH_3$	2:1	2	98	95
3	$CH_3CH_2CH_2OH$	$ArCO_2CH_2CH_2CH_3$	2:1	2	95	93
4	$CH_3CH_2CH_2CH_2OH$	$ArCO_2CH_2CH_2CH_2CH_3$	2:1	2	99	97
5	$(CH_3)_2CHOH$	$ArCO_2CH(CH_3)_2$	2:1	2	80	91
6	$(CH_3)_3COH$	$ArCO_2C(CH_3)_3$	2:1	overnight	99	80
7	CH_2=$CHCH_2OH$	$ArCO_2CH_2CH$=CH_2	2:1	2	84	95
8	C_6H_5OH	$ArCO_2C_6H_5$	2:1	15	78	80
9	C_6H_3OH	$ArCO_2C_6H_3(CH_3)_2$–6,2	2:1	15	83	82

Table 4. Synthesis of *n*-butyl esters of the various carboxylic acids with Ph_3PBr_2 and Ph_3PI_2 in the presence of DMAP in dichloromethane at room temperature.

Entry	Acid	Ester	Mole ratio DMAP:Acid	Reaction Time (min)	Yield (%) Ph_3PBr_2	Yield (%) Ph_3PI_2
1			2.5:1	2	87	90
2			2:1	2	99	97
3			2.5:1	2	91	92
4			2.5:1	2	90	90
5			2:1	2	90	90
6			2:1	3	89	92
7			2:1	2	93	94
8			2:1	2	80	80
9			2.5:1	2	90	93
10			2.5:1	2	90	92
11	$CH_3(CH_2)_8CO_2H$	$CH_3(CH_2)_8CO_2Bu\text{-}n$	2.5:1	2	91	81
12			4:1	2	95	95
13	$(CH_3)_2CHCH_2COCO_2H$	$(CH_3)_2CHCH_2COCO_2Bu\text{-}n$	2.5:1	2	90	90

Entry	Acid	Ester	Mole ratio DMAP:Acid	Reaction Time (min)	Yield (%) Ph_3PBr_2	Yield (%) Ph_3PI_2
14	$(CH_3)_3CCO_2H$	$(CH_3)_3CCO_2Bu\text{-}n$	2.5:1	15	49	48
15			2:1	15	55	60
16			2:1	60	85	90

corresponding n-butyl ester with Ph_3PBr_2 and Ph_3PI_2 in 55 and 60% yields respectively (Table 4, entry 15). Phthalic acid reacted with *n*-butanol in the presence of Ph_3PI_2 or Ph_3PBr_2 and DMAP (mole ratio, 1:2:2:4) to provide dibutyl phthalate in excellent yield in dichloromethane at room temperature (Table 4, entry 12).

Aliphatic carboxylic acids such as 3-phenylpropanoic acid, decanoic acid, 4-methyl-2-oxo-pentanoic acid and indole-3-butyric acid (Table 4, entries 10, 11, 13, and 16) also afforded the corresponding butyl esters with Ph_3PI_2 or Ph_3PBr_2 in the presence of DMAP in excellent yields (molar ratio DMAP:acid = 2.5:1). Even 2,2-dimethylpropanoic acid as a highly sterically hindered aliphatic acid underwent the esterification reaction with both reagents in moderate yields (entry 14). *trans*-Cinnamic acid was also converted to the corresponding butyl ester in excellent yield, without double bond bromination (entry 9).

3. Conclusions

We have introduced an efficient one-pot method for esterification of carboxylic acids with cheap and readily available Ph_3PI_2 and Ph_3PBr_2 under neutral and very mild conditions in the presence of DMAP. The advantages of the present method are very short reaction times and good to excellent yields. Furthermore, by this method one can prepare esters of highly hindered carboxylic acids and alcohols. Although DMAP is used in two-fold excess relative to the each carboxylic group, 80% to 90% of DMAP is recovered by aqueous extraction after completion of the reaction and further extraction of alkaline solution by dichloromethane.

4. Experimental

4. 1. General

^1H and ^{13}C NMR spectra were recorded on Bruker Advance DPX FT spectrometer at 250 and 62.9 MHz, respectively, and with TMS as an internal standard. IR spectra were obtained on a Perkin-Elmer FTIR-800 instrument. Mass spectra were obtained on a Shimadzu GCMS0QP 1000EX at 20 and/or 70 eV, and elemental analyses were performed on Thermofinnigan 1112 flash EA. The synthesized esters were characterized with IR, ^1H, and ^{13}C NMR spectroscopy and mass spectrometry, and CHN analysis.

4. 2. Typical Procedure for the Esterification of Carboxylic Acids

4. 2. 1. Using Ph_3PI_2

To a solution of Ph_3P (0.39 g, 1.5 mmol) and I_2 (0.38 g, 1.5 mmol) in 5 ml of CH_2Cl_2 was added 4-methoxybenzoic acid (0.23 g, 1.5 mmol) and DMAP (0.45 g, 3.7 mmol). The solution was stirred for 5 min at room temperature and then *n*-butanol (0.14 ml, 1.5 mmol) was added. TLC monitoring showed that the reaction was completed after 2 min (plates: aluminum-backed silica gel, Merck 60 GF254). The crude product was purified by short-column chromatography on silica gel with *n*-hexane/ethyl acetate (4:1) to provide pure *n*-butyl 4-methoxybenzoate (0.29 g, 90%) as a yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 0.82(t, 3H, CH_3), 1.27 (m, 2H, CH_2CH_3), 1.55 (m, 2H, OCH_2CH_2), 3.69 (s, 3H, OCH_3), 4.14 (t, 2H, OCH_2), 6.75 (d, 2H, ArH), 7.85 (d, 2H, ArH); ^{13}C NMR ($CDCl_3$, 69.9 MHz): δ 13.70, 18.97, 30.79, 55.24, 64.39, 113.98, 122.88, 131.43, 163.21, 166.29; IR (KBr): ν 1714.6 (C=O), 1256.6 (C–O) cm^{-1}; MS (EI, 70eV): m/z (%) 208 (M^+, 7), 151(0.7), 135 (100), 107 (13.6), 92 (20.2), 76(5.5). Elemental Anal.(%): Calcd. for $C_{12}H_{16}O_3$: C 69.21, H 7.74. Found: C 70.7, H 7.81.

4. 2. 1. Using Ph_3PBr_2

Ph_3P (0.26 mg, 1 mmol) and Br_2 (0.05 ml, 1 mmol) were added to 5 ml of cold CH_2Cl_2 on ice bath. 4-Nitrobenzoic acid (0.167 g, 1 mmol) and DMAP (0.24 g, 2

mmol) were added to this solution and the solution was stirred for 3 min on ice bath, and allowed to be warmed up to room temperature. After that phenol (0.094 g, 1 mmol) was added. TLC monitoring showed that the reaction was completed after 15 min (plates: aluminium-backed silica gel, Merck 60 GF_{254}). The crude product was purified on the short-column of silica gel with *n*-hexane/ethyl acetate (4:1) to provide pure phenyl 4-nitrobenzoate (0.19 g, 78%) as a white solid. M.p. = 105 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.21 (t, 1H, phenol), 7.22 (d, 2H, phenol), 8.33 (d, 2H, ArH), 8.41 (d, 2H, ArH); ^{13}C NMR ($CDCl_3$, 69.9 MHz): δ 121.40, 123.71, 126.40, 129.67, 131.28, 134.98, 150.51, 150.91, 167.60; IR (KBr): ν 1739.7 (C=O), 1270 (C–O) cm^{-1}; MS (EI, 70eV): *m/z* (%) 243 (M^+, 9.3), 167 (0.2), 150 (100), 122 (0.8), 104, 76. Elemental Anal.(%): Calcd. for $C_{13}H_9NO_4$: C 64.20, H 3.73, N 5.76. Found: C 64.08, H 3.68, N 5.62.

5. Acknowledgment

Shiraz university research council are gratefully acknowledged for the support of this study.

6. References

1. J. Otera, *Esterification: Methods, Reactions and applications,* Wiley-VCH, Verlag GmbH & Co. KGaA. Weinheim, **2003**.
2. a) A. Buzas, C. Egnell, P.C. R. Freon, *Acad. Sci.* **1962**, *255*, 945–947. b) M. Nahmany, A. Melman, *Org. Lett.* **2001**, *3*, 3733–3735. c) H. Zhao, A. Pendri, R. B. Greenwald, *J. Org. Chem.* **1998**, *63*, 7559–7562.
3. a) O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382. b) D. L. Hughs, R. A. Reamer, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1998**, *110*, 6487–6491. c) C. Ahn, R. Correia, P. DeShong, *J. Org. Chem.* **2002**, *67*, 1751–1753. d) C. Ahn, P. DeShong, *J. Org. Chem*. **2002**, *67*, 1754–1758.
4. a) S. Hashimoto, I. Furukawa, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2227–2228. b) J. M. Aizpura, C. Palomo, *Synthesis*, **1982**, 684–686. c) K. Sucheta, G. S. R. Reddy, D. Ravi, N. R. Rao, *Tetrahedron Lett.* **1994**, *35*, 4415–4416. d) R. C. Rodrigues, I. M. A. Barros, E. L. S. Lima, *Tetrahedron Lett.* **2005**, *46*, 5945–5947. e) S. Torii, H. Okumoto, M. Fujikawa, M. A. Rashid, *Chem. Express*, **1992**, *7*, 933–936.
5. T. Tsunoda, F. Ozaki, S. Ito, *Tetrahedron Lett.* **1994**, *35*, 5081–5082.
6. Z. M. Jaszay; I. Petnehazy; L. Toke, *Synth. Commun.* **1998,** *28,* 2761–2758.
7. J. McNulty, S. Cheekoori, J. J. Nair, V. Larichev, A. Caprtta, A. L. J. Robertson, *Tetrahedron Lett*. **2005**, *46*, 3641–3644.
8. S. Shoda, T. Mukaiyama, *Chem. Lett*, **1980,** 391–392.
9. a) S. Chandrasekaran, J. V. Turner, *Synth. Commun.* **1982**, *12*, 727–731. b) J. H. Berwster, C. J. Jr. Ciotti, *J. Am. Chem. Soc.* **1955**, *77*, 6214–6215. c) K. Wkasugi, A. Nakamura, Y. Tanabe, *Tetrahedron Lett.* **2001**, *42*, 7427– 7430.
10. D. G. Niyogi, S. Singh, R. D. Verma, *J. Fluorine Chem.* **1994**, *68*, 237–238.
11. a) N. Tamayo, A. M. Echavarren, M. C. Paredes, *J. Org. Chem.* **1991**, *56*, 6488–6491. b) J. S. Kiely, E. Laborde, I. E. Lesheski, R. A. Busch, *J. Heterocycl. Chem.* **1991**, *28*, 1581–1585. c) F. D'Aniello, D. Mattii, M. Taddei, *Synlett*, **1993,** 119–121.
12. M. Ballester-Rodes, A. L. Palomo-Coll, *Synth. Commun*. **1984**, *14*, 515–520.
13. M. H. Kim, D. V. Patel, *Tetrahedron Lett.* **1994**, *35*, 5603–5606.
14. T. Mukaiyama, F.-C. Pai, M. Onaka, K. Narasaka, *Chem. Lett*. **1980**, 563–566.
15. J. J. Folmer, S. M. Weinreb, *Tetrahedron Lett.* **1993**, *34*, 2737–2740.
16. M. Ueda, H. Oikawa, T. Teshirogi, *Synthesis*, **1983,** 908–909.
17. A. Ouihia, L. Rene, J. Guilhem, C. Pascard, B. Badet, *J. Org. Chem.* **1993**, *58*, 1641–1642.
18. M. Kunishima, J. Morita, C. Kawachi, F. Iwasaki, K.Terao, S. Tani, *Synlett*, **1999**, 1255–1256.
19. K. R. Haynes, M. Holden, *Aust. J. Chem*. **1982**, *35*, 517–524.
20. T. Y. S. But, P.H. Toy, *J. Am. Chem. Soc.* **2006**, *128*, 9636–9637.
21. S. Dandapani, D. P. Curran, *J. Org. Chem.* **2004**, *69*, 8751–8757.
22. C. Salome, H. Kohn, *Tetrahedron,* **2009**, *65*, 456–460.

Povzetek

Avtorji v prispevku poročajo o pripravi estrov alifatskih in aromatskih karboksilnih kislin z dobrimi izkoristki v prisotnosti bodisi trifenilfosfin dibromida ali trifenilfosfin dijodida ter N,N-dimetilaminopiridina v diklorometan kot topilu pri sobni temperaturi.