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A Simple, Efficient, Green, Cost Effective and Chemoselective Process for the Esterification of Carboxylic Acids

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Abstract:

Carboxylic acids have been esterified under mild and solvent-free conditions in high yield and purity using the green reagents, dimethyl carbonate and diethyl carbonate, under acid catalysis. The present methodology is free of the disadvantages of base catalysis described earlier, such as high temperatures, use of autoclaves, use of the expensive DBU as base in stoichiometric amounts and the carbonate as solvent. High chemoselectivity is observed in the case of hydroxybenzoic acids.

Introduction

Esters[1] are encountered in various roles in all areas of synthetic organic chemistry, and making them efficiently is of paramount importance. General methods available start from carboxylic acids which are directly condensed with alcohol under acid catalysis (Fischer esterification), activated and then used for acylation of alcohols or converted to salts and the carboxylates treated with alkylating agents. These methods, in spite of their exceptional utility, suffer from a severe environmental burden. Fischer esterification is an equilibrium process catalyzed by strong, corrosive, mineral acids. The water generated in the reaction has to be continuously removed (not very effective) by azeotroping or by use of a dehydrative agent or its role countered by use of a large excess of the alcohol. Methanol and ethanol can generate genotoxic alkyl sulphuric acids. Acylation and alkylation are inherently polluting because of salt generation, use of toxic catalysts and reagents and use of chlorinated solvents.

There have been attempts to make Fischer esterification highly atom economical and practically very convenient. An ideal esterification has been defined[2] as one with a 1:1 acid/alcohol stoichiometry, a neutral catalyst, no dehydrative agent and yields and conversions being 100%. Several catalysts[3] have been evolved to achieve high yields with equimolar acid and alcohol, for example, graphite bisulphate $C_{24}HSO_4\cdot2H_2SO_4$,[3a] B_2O_3/PTS,[3b] $TiCl(OTf)_3/(Me_2SiO)_4$,[3c] $NaHSO_4\cdot H_2O$,[3d] $HfCl_4\cdot2THF$ or $ZrCl_4\cdot2THF$, $HfOCl_2\cdot8H_2O$ or $ZrOCl_2\cdot8H_2O$,[3e] Ph_2NH_2TfO,[3f] *p*-dodecylbenzenesulphonic acid,[3g] fluorous distannoxane,[3h] Ti^{IV} on K-10,[3i] $4\text{-}NO_2C_6H_4NH_2C_6H_5TfO$,[3j] $Ti(O)(acac)_2$,[3k] H_3BO_3,[3l] Bronsted acidic ionic liquids,[3m] $K_5CoW_{12}O_{14}\cdot3H_2O$,[3n] $(Mes)_2NH_2C_6F_5SO_3$,[3o] and $FeCl_3\cdot6H_2O$.[3p] While yields are generally high, there are limitations to this strategy: need to use a solvent, need to azeotrope,[3e,k] high temperatures,[3e,h] long reaction times,[3g] lack of general applicability except in two cases,[3k,n] difficulty in using MeOH or EtOH, use of a dehydrative agent,[3a,c] extensive drying of recovered ionic liquids,[3m] etc.

In the last two decades, dimethyl carbonate (DMC)[4] has gained prominence as a green reagent in base-catalyzed methylation or methoxycarbonylation of anilines, phenols, active methylene compounds and carboxylic acids. The uniqueness of DMC lies in the fact that it is nontoxic and gives rise only to CO_2 (nontoxic) and MeOH (recoverable). However, it is inherently not as reactive as Me_2SO_4 or MeX as an alkylating agent in a $B_{AL}2$-type mechanism. As a consequence, higher temperatures (160−300 °C)[5] under base catalysis are essential. The Novartis group has made a significant contribution to this area by the use of 1 equiv of DBU as a base in alkylation of carboxylic acids with DMC used as a solvent at reflux.[6] DBU was found to activate DMC, resulting in a lower temperature

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(1) (a) Otera, J. *Chem. Rev.* **1993**, *93*, 1449. (b) Franklin, A. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2451. (c) Otera, J. *Esterification Methods, Reactions and Applications*; Wiley VCH: Weinheim, 2003. (d) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999. (e) Newman, M. S. *J. Am. Chem. Soc.* **1941**, *63*, 2431.

(2) Otera, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2044.

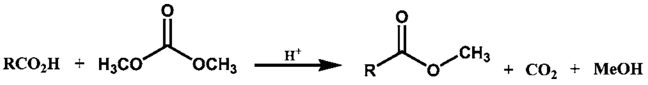
(3) (a) Bertin, J.; Kagan, H. B.; Luche, J. L.; Setton, R. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (b) Carlson, C. G.; Hall, J. E.; Huang, Y. Y.; Kotila, S.; Rauk, A.; Tavares, D. F. *Can. J. Chem.* **1987**, *65*, 2461. (c) Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, *24*, 141. (d) Li, Y.-Q. *Synth. Commun.* **1999**, *29*, 3901. (e) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140. Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8179. Nakayama, M.; Sato, A.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2004**, *346*, 1275. (f) Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249. (g) Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101. (h) Xiang, J.; Orita, A.; Otera, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4117. (i) Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2003**, *44*, 9205. (j) Liu, X.-G.; Hu, W.-X. *J. Chem. Res.* **2004**, 564. (k) Chen, C.-T.; Munot, Y. S. *J. Org. Chem.* **2005**, *70*, 8625. (l) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5047. only for α-hydroxycarboxylic acids. (m) Ganeshpure, P. A.; George, G.; Das, J. *Arkivoc* **2007**, 273. Joseph, T.; Sahoo, S.; Halligudi, S. B. *J. Mol. Catal. A: Chem.* **2005**, *234*, 107. Zhang, H.; Xu, F.; Zhou, X.; Zhang, G.; Wang, C. *Green Chem.* **2007**, *9*, 1208. (n) Bose, D. S.; Satyender, A.; RudraDas, A. P.; Mereyala, H. B. *Synthesis* **2006**, 2392. (o) Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686. (p) Komura, K.; Ozaki, A.; Ieda, A.; Sugi, Y. *Synthesis* **2008**, 3407.

(4) (a) Tundo, P.; Selva, M. *Acc. Chem. Res.* **2002**, *35*, 706. (b) Mauri, M. M.; Romano, U.; Rivetti, F. Q. *Ing. Chim. Ital.* **1985**, *21*, 6. (c) Shaikh, A.-A. G.; Sivaram, S. *Chem. Rev.* **1996**, *96*, 951. (d) Ono, Y. *Pure. Appl. Chem.* **1996**, *68*, 367. (e) Collier, S. J. *Sci. Synth.* **2006**, *20.5*, 1. (f) Lissel, M.; Dezfuli, A. R. R. *Kontakte (Darmstadt)* **1990**, 20. (g) Shieh, W.-C.; Dell, S.; Bach, A.; Repič, O.; Blacklock, T. J. *J. Org. Chem.* **2003**, *68*, 1954. (h) Parrish, J. P.; Salvatore, R. N.; Jung, K. W. *Tetrahedron* **2001**, *56*, 8207.

(5) (a) PGG Industries, Pittsburg, PA, U.S.A. U. S. Patent 4,513,146. 1985. (b) *Anonymous Research Disclosure, U.S.A.*; 241210, **1984**. (c) Lee, Y.; Shimizu, I. *Synlett* **1998**, 1063.

10.1021/op900096y CCC: $40.75

Scheme 1. **Esterification of carboxylic acids using DMC**



for reaction (90 °C). But the use of 1 equiv of an expensive base, such as DBU, and DMC as a solvent is to be regarded as drawbacks.

Only two examples could be found in the literature for acid-catalyzed esterifications using DMC. In one case, $PTSA \cdot H_2O$ was used at 170 °C, and in the other, acidic zeolites ($H\beta$ and HZSM-5) at 160 °C[8] were used, with yields dependent on the pore size of zeolites. An amphoteric zeolite (NaY Faujasite) has also been used.[9] Expensive dialkyl dicarbonates (pyrocarbonates) in the presence of catalytic ($Mg(ClO_4)_2$[10] or DMAP[11] (esp. for *tert*-butyl esters) were also found to be quite effective for esterification. Catalytic $MgCl_2 \cdot 6H_2O$[12] permitted the preparation of *tert*-butyl esters as well as methyl and ethyl esters from the corresponding dicarbonates.

Results and Discussion

It seemed reasonable to expect DMC to get protonated by a strong acid such as H_2SO_4 and thereby initiate the esterification process at moderate temperatures. In such a process a carboxylic acid functions as a nucleophile unlike in the Fischer esterification, where it functions as an electrophile after protonation. At the time we started this study we were unaware of the acid-catalyzed study on DMC which might, in fact, have discouraged us from further investigation.

We now report[13] the first mild (80−90°), efficient and solvent-free esterification of carboxylic acids under acid catalysis by the green reagent, DMC. The preferred catalyst is conc. H_2SO_4 (0.025−0.1 equiv). PTSA is an efficient alternative but at a 0.2 equiv level. A remarkable outcome of the present work (Scheme 1) is the high yield of product (up to 99%) in most cases with very high purity (95−>99%) after a simple workup without any purification step involved.

Optimized experiments using *m*-toluic acid (MTA) and *o*-toluic acid (OTA) and 1.8 equiv of DMC are shown in Table 1. Concentrated H_2SO_4 (96%) at 0.1 equiv level and PTSA (anhydrous or hydrate) at 0.2 equiv level are catalysts of choice. Higher loadings of the catalysts reduced reaction times, while lower amounts of acid catalysts increased the reaction time but not to a great extent (entry 3,4), thus permitting use of 2.5 mol % H_2SO_4. Small amounts of acetic acid (0.1−0.2 equiv) helped increase mobility of the reaction mixture without affecting yields or purity.

Surprisingly, aq H_2SO_4 (72%) was quite effective but at the expense of reaction time (entry 8). The most effective catalyst was triflic acid (entry 15). Even the Lewis acid $TfOSiMe_3$, was quite efficient (not shown).[14] Silica-sulfuric acid[15] was as effective as H_2SO_4 but not quite efficient after recovery and one recycle. Highly inactive catalysts were: NH_2SO_3H, $NaHSO_4 \cdot H_2O$, $Zn(OTf)_2$, $BiCl_3$, $BF_3 \cdot Et_2O$, PyH^+TfO^- and anhydrous H_3PO_4. Workup is by quenching into aqueous $NaHCO_3$ and extracting the product into ethyl acetate. Part of excess DMC along with MeOH can be recovered by direct distillation from the reaction mixture before or after workup.

The present method has general applicability for aromatic, aliphatic, cinnamic, nicotinic and aminobenzoic acids (Table 2). Reactivity differences between aromatic and aliphatic acids are negligible, and the longer times with nitrogen-containing acids are, to a considerable degree, due to a solubility problem. Method A is for monocarboxylic acids reacting with 1.8 equiv of DMC in the presence of 0.1 equiv of H_2SO_4 or 0.2 equiv of PTSA (anhydrous or hydrate) with or without 0.1 equiv of added AcOH at 80−85° or at reflux (100°, bath). Method B is for dicarboxylic acids reacting with 3.6 equiv of DMC in the presence of 0.2 equiv of H_2SO_4 (for a faster reaction) to give diesters. Method C is for nitrogen-containing acids reacting with 3.6 equiv of DMC and 1.4 equiv of H_2SO_4.

Terephthalic acid, thiosalicyclic acid, phenylglycine, and phenylalanine did not react at all because of high insolubility. Sterically hindered benzoic acid (entry 10) gave a 74.5% yield while pivalic acid (entry 24) did not react at all. It is interesting to note that for sterically hindered carboxylic acids the recommended procedure consists in dissolution of the acid in 100% H_2SO_4 and adding the solution into a desired alcohol.[1e] Very high chemoselectivity was observed with hydroxybenzoic acids (entries 11, 12). Methyl paraben (entry 12) was thus prepared in high yield and purity. A similar high selectivity was observed with diethyl carbonate (DEC) even at 120 °C to give ethyl paraben (Table 3). Such a selectivity was also observed frequently under acidic[16] and basic[17] conditions. The phenolic group in 4-chlorophenol and hydroquinone were untouched under the present conditions using DMC or DEC. The naphthols, however, gave excellent yields of methyl ethers[18] (see Experimental Section). An interesting case of chemoselective methoxycabonylation of aliphatic OH in hydroxyalkyl-substituted phenols in the presence of a catalytic amount of H_2SO_4 in DMC as solvent has been reported recently.[19]

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(6) (a) Shieh, W.-C.; Dell, S. J.; Bach, A.; Repič, O. *J. Org. Chem.* **2002**, *67*, 2188. (b) Shieh, W.-C.; Dell, S. J. U.S. Patent 6,515,167 B1, 2003. (c) Shieh, W.-C.; Lozanov, M.; Loo, M.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **2003**, *44*, 4563; 135 °C reaction temperature with benzylcarbonate and Dabco.

(7) Heuer, L.; Joentgen, W.; Klausener, A. DE 4311424, 1994.

(8) Kirumakki, S. R.; Nagaraju, N.; Chary, K. V. R.; Narayanan, S. *Appl. Catal., A* **2003**, *248*, 161. (b) Kirumakki, S. R.; Nagaraju, N.; Murthy, K. V. V. S. B. S. R.; Narayanan, S. *Appl. Catal., A* **2002**, *226*, 175. (c) Reddy, B. M.; Sreekanth, P. M.; Reddy, V. R. *J. Mol. Catal. A: Chem.* **2005**, *225*, 71.

(9) Selva, M.; Tundo, P. *J. Org. Chem.* **2006**, *71*, 1464.

(10) (a) Tarbell, D. S.; Leister, N. A. *J. Org. Chem.* **1958**, *23*, 1149. Leister, N. A.; Tarbell, D. S. *J. Org. Chem.* **1958**, *23*, 1152 (for a discussion of the stability and reactivity). (b) Goossen, L.; Dohring, A. *Adv. Synth. Catal.* **2003**, *345*, 943. (c) For a similar selective activation of a dicarbonate with $Mg(ClO_4)_2$ in the synthesis of aryl ethyl carbonates, see: Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Palazzi, P.; Sambri, L. *Eur. J. Org. Chem.* **2006**, 4429.

(11) Mandal, A. B.; Bhat, S. N.; Sambasivan, G., Kodange, G.; Sridharan, M. American Chemical Society National Meeting, Chicago, IL, U.S.A., August 26−30, 2001.

(12) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Synthesis* **2007**, 3489.

(13) Someswara Rao, C.; Subbaraju, G. V.; Satyanarayana, C. Aptuit Laurus, Hyderabad. Indian Patent Appl. No. 296/CHE/2009, 2009.

(14) Reaction of *m*-toluic acid with 1.8 equiv of DMC at 80−85 °C/10 h using 0.1 equiv of $CF_3SO_3SiMe_3$ gave rise to the ester product in 92% yield and 98% purity. It may be noted in this connection that trimethylsilyl carboxylates are totally unreactive in the present work.

(15) Zolfigol, M. A. *Tetrahedron* **2001**, *57*, 9509.

Table 1. **Optimization of the acid catalyst in DMC-mediated esterification**

s. no.	substrate[a]	catalyst (equiv)	temp (°C)[b]	time (h)[c]	yield (%)[d]	purity (%)[e]
1	OTA	H_2SO_4 (0.1)	80−85	8.5	92.5	99.59
2	OTA	H_2SO_4 (0.1)	100	6.5	97.0	99.74
3	OTA	H_2SO_4 (0.05)	100	10	92.5	99.93
4	OTA	H_2SO_4 (0.025)	100	13	87.0	96.20
5	OTA	H_2SO_4 (0.2)	100	3	94.7	99.94
6	OTA	H_2SO_4 (1)	100	1	99.95	97.80
7	OTA	H_2SO_4 (0.1)/AcOH	80−85	9.5	94.3	99.14
8	OTA	H_2SO_4 (0.1)/H_2O(0.2)	80−85	24	97.0	98.75
9	MTA	silica-OSO_3H (0.1)	80−85	6	97.0	98.83
10	MTA	PTSA anhyd. (0.1)	80−85	14	98.5	97.0
11	MTA	PTSA anhyd. (0.2)	80−85	6	98.0	97.0
12	MTA	PTSA H_2O (0.1)	80−85	12[f]	71.0	97.8
13	MTA	PTSA H_2O (0.2)	100	5	98.3	98.0
14	MTA	CH_3SO_3H (0.1)	80−85	16	98.0	99.5
15	MTA	CF_3SO_3H (0.1)	80−85	3.5	95.11	99.2

[a] 5 g batch size. [b] Bath temp. [c] Time for completion (TLC). [d] After workup with aq $NaHCO_3$ and EtOAc. [e] By HPLC area %. [f] Incomplete reaction.

Table 2. **Reaction of RCO_2H with DMC under catalysis by conc. H_2SO_4**

s. no.	substrate[a], R=	method	time (h)	isolated yield (%)	% purity[b]
1	Ph	A	8	93.89	99.8
2	2-$CH_3C_6H_4$	A	8.5	92.55	99.59
3	3-$CH_3C_6H_4$	A	9	99.4	99.5
4	4-$CH_3C_6H_4$	A	10	95.7	98.62
5	4-$NO_2C_6H_4$	A	9.5	94.2	97.02
6	4-MeO C_6H_4	A	16	95.2	98.31
7	3,5-$(MeO)_2$ C_6H_3	A	6	99.9[c]	99.56
8	4-$PhC_6H_4CH_2$	A (reflux)[d]	22	84.5	99.49
9	2-(4-$CH_3C_6H_4$)C_6H_4	A (reflux)[d]	10	75.23	98.2
10	2,6-$Me_2C_6H_3$	A	8	74.50	99.95
11	2-OH-C_6H_4	A	22	92.7	99.72
12	4-OH-C_6H_4	A	7.5	97.6[e]	99.77
13	Ph CH═CH	A	13	91.4	97.65
14	2-$CO_2HC_6H_4$	B	11	99.8	99.59
15	2-furyl	A	7.5	92.4	96.9
16	2-$NH_2C_6H_4$	C	20	64.6	99.86
17	4-$NH_2C_6H_4$	C	12	87.9[f]	97.39
18	3-pyridyl	C (reflux)	22	54.7	99.86
19	4-pyridyl	C (reflux)	17	67.5	99.89
20	$PhCH_2$	A	5.5	97.09	97.33
21	Ph_2CH	A	3.5	97.5	98.46
22	CH_2CO_2H	C	2	99.8[g]	95.46
23	$CH_3(CH_2)_3CHEt$	A	10	99.2	99.2
24	*t*-Bu	A	9	−[h]	−
25	$PhCH_2CH_2$	A	5	99.8	99.22

[a] 5 g batches. [b] By HPLC or GC. [c] Pale yellow solid; mp 35−38 °C (rep 31−33 °C). [d] 0.1 equiv of AcOH added to facilitate stirring. [e] Mp 125−127 °C (rep 126−128 °C). [f] Off-white solid; mp 109−110 °C (rep 110−111 °C). [g] Diester, even with 1.8 equiv of DMC. [h] No reaction.

Table 3. **Reaction of RCO_2H with diethyl carbonate (1.8 equiv) at 110−120° C (bath) in presence of H_2SO_4(0.1 equiv)**

s. no.	R	time (h)	isolated yield (%)	purity (%)
1	2-$CH_3C_6H_4$	13	99	99.8
2	2-$CH_3C_6H_4$	10[a]	94.5	96.7
3	$PhCH_2CH_2$	6	98.6	98.75
4	4−$OHC_6H_4CH_2$	2.5	9.0	97.9
5	3,5-$(OH)_2C_6H_3$	3	89	99.4[b]

[a] 5 h using 1.3 equiv of DEC and 0.5 equiv of conc. H_2SO_4. [b] White solid; mp 127−129 °C (rep 127−130 °C); 5.47 equiv of DEC was used along with 0.1 equiv of AcOH.

Diethyl carbonate (DEC) was much less reactive than DMC at 80−85 °C but proved to be as effective at 110−120 °C. Using 1.8 equiv of DEC and 0.1 equiv of H_2SO_4 high yields of ethyl esters could be obtained in high purity (Table 3). It is interesting to note a temperature effect on catalytic activity of PyH^+TfO^-. This catalyst was quite effective with DEC at 110−120°/6 h in the case of phenylpropionic acid giving rise to the ethyl ester in 97% yield and 98% purity. It was, however, totally ineffective towards DMC at 80−85 °C.

Cost Effectiveness. The process reported in this communication is more cost-effective for methyl and ethyl esters and practically more convenient than the normal Fischer esterifcation process using MeOH or EtOH as solvent. The recovered solvent in the Fischer process accumulates water progressively on recycling and becomes increasingly ineffective. Genreation of genotoxic alkyl sulphuric acid is of serious concern in the Fischer process. The present process is also superior to the equimolar acid and alcohol strategy discussed in the introduction particularly because of the absence of a solvent, absence of water as a by product and the general applicability to many structural types of carboxylic acid. More importantly, it is so easy to scale up, and the productivity factor will be very high since there is no solvent and the reaction times are reasonably short. (See Experimental Section.)

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(16) (a) *Chem. Abstr* **1984**, *100*, 174379. (b) *Chem. Abstr.* **1979**, *90*, 186616, Spanish Patent. (c) Chakraborti, A. K.; Basak, A.; Grover, V. *J. Org. Chem.* **1999**, *64*, 8014. (d) *Chem. Abstr.* **1985**, *102*, 5860q. (e) Pavlov, S.; Bogavac, M.; Arsenijevic, L.; Arsenijevic, V. *Arch. Farm* **1986**, *36*, 161. *Chem. Abstr.*, **1987**, *107*, 154023. (f) Das, B.; Venkataiah, B.; Madhusudhan, P. *Synlett* **2000**, 59. (g) Mal, D. *Synth. Commun.* **1986**, *16*, 331. (h) *Chem. Abstr* **1986**, *104*, 88298; East German Patent. (i) *Chem. Abstr* **1985**, *103*, 214999; Jpn. Patent. (j) Jaszay, Z. M.; Petnehazy, I.; Toke, L. *Synthesis* **1989**, 745. (k) *Chem. Abstr* **1989**, *110*, 23456. (l) Srinivas, K. V. N. S.; Das, B. *J. Org. Chem.* **2003**, *68*, 1165.

(17) (a) Rama Rao, A. V.; Deshmukh, M. N.; Sivadasan, L. *Chem. Ind.* **1981**, 164. (b) Ambika; Singh, P. P.; Chauhan, S.M. S. *Synth. Commun.* **2008**, *38*, 928. (c) Biondini, D.; Brinchi, L.; Germani, R.; Savelli, G. *Lett. Org. Chem.* **2006**, *3*, 207. (d) *Chem. Abstr.* **1986**, *104*, 88298; East German Patent. (e) Barry, J.; Bram, G.; Decodts, G.; Loupy, A.; Orange, C.; Petit, A.; Sansoulet, J. *Synthesis* **1985**, 40. (f) Artus, J. J. *Chem. Abstr.* **1979**, *90*, 186616s; Spanish Patent. (g) Guo, W.; Li, J.; Fan, N.; Wu, W.; Zhou, P.; Xia, C. *Synth. Commun.* **2005**, *35*, 145.

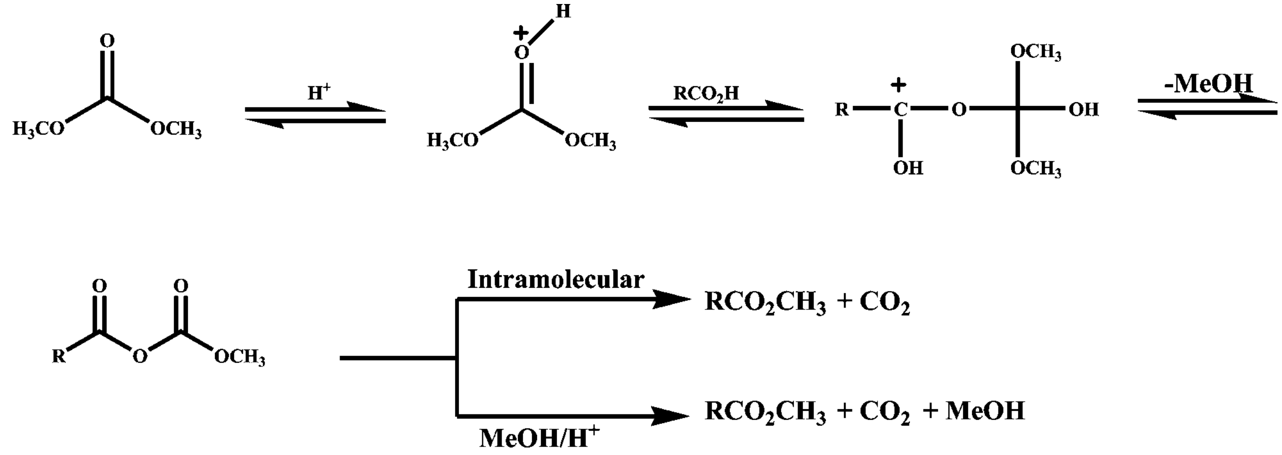
(18) (a) Someswara Rao, C. *The Chemistry of Process Development in Fine Chemical and Pharmaceutical Industry*, 2nd ed.; John Wiley & Sons Ltd.: U.K., and Asian Books Pvt. Ltd.: New Delhi, 2006; p 511. (b) For a recent use of DMC in methylation of β-naphthol using a phosphonium ionic liquid (IL 103 of Cytec, Canada), see: Yadav, G. D.; Pavankumar, A. 11th Annual Green Chemistry Engineering Conference, Washington, DC, June 26−29, 2007.

(19) Bernini, R.; Mincione, E.; Crisante, F.; Barontini, M.; Fabrizi, G.; Gentili, P. *Tetrahedron Lett.* **2007**, *48*, 7000.

Table 4. **Reaction of RCO_2H with reduced amounts of carbonate in the presence of added methanol or ethanol**

s. no.	substrate	carbonate (equiv)	MeOH/ EtOH (equiv)	time (h)	temp (° C)	yield (%)	purity (%)
1	$4\text{-}OHC_6H_4CO_2H$	DMC (0.66)	3.3/−	24	90	88	99.93
2	$4\text{-}OHC_6H_4CO_2H$	DEC (0.66)	−/2.3	24	100	97.22	99.41
3	$PhCH_2CH_2\ CO_2H$	DMC (0.66)	0.33/−	9	90	92.3	99.62

Scheme 2. **Possible mechanism for DMC-mediated esterification (under acid catalysis)**



To reduce the costs even further a new strategy was evolved (Method D). It consists of using a synergistic combination of DMC−MeOH or DEC−EtOH in a 0.66−0.33 to 3.3 equiv ratio (Table 4). Consumption of the carbonate is thereby drastically reduced. The well-known Fischer esterification mechanism may be operating here along with the mechanism for carbonate-mediated esterification (Scheme 2).

A likely reaction mechanism for carbonate-mediated esterification based on earlier studies (refs 8b and 10) is shown in Scheme 2. Protonated DMC reacts with RCO_2H (a nucleophile), giving rise to the reactive acyloxy methyl carbonate intermediate (mixed carbonic acid anhydrides)[10a] which can give rise to the ester by an intramolecular route or intermolecularly by reaction with MeOH. An attempt to distinguish between these two pathways was inconclusive.[10b] Such intermediates are known to be involved in the reaction of carboxylic acids with alkyl chloroformates,[20−22] with dialkyl dicarbonates[10b,c] with dimethyl carbonate[8,9] and with activated carbamates such as EEDQ[23] and BBDI.[24]

Conclusion

A green, solvent-free, highly efficient and very cost-effective esterification method under mild conditions using dimethyl and diethyl carbonates has been developed using H_2SO_4 and PTSA as catalysts. The crude isolated yields and purities of ester products are remarkably high. This method is free of the disadvantages of DMC-mediated esterifications under base catalysis, the regular Fischer esterification process using methanol or ethanol in large excess and also the recent modification of the Fischer process using equimolar acid and alcohol in presence of various catalysts. It is very easily scalable to any level without any effect on yield and purity.

Experimental Section

All products are characterized by IR and NMR spectra and purities checked by HPLC or GC (area % values). Reaction monitoring was done by TLC on silica gel plates or by GC. Reaction temperatures refer to oil bath temperatures.

Method A: Methyl *o*-Toluate (Representative Procedure for Monocarboxylic Acids). A mixture of *o*-toluic acid (50 g, 0.367 mol), dimethyl carbonate (55.6 mL, 0.661 mol) and conc. H_2SO_4 (96%) (1.9 mL, 0.0342 mol, 9.32 mol %) was heated under magnetic stirring at 80−85 °C for 8.5 h. TLC (20% EtOAc in hexane) showed only traces of unreacted acid. On cooling the homogeneous reaction mixture to room temperature a small volume of a brown layer separated out. The reaction mixture was poured into 10% aq $NaHCO_3$ (30.8 g in 300 mL water) under stirring. The product was extracted into EtOAc or CH_2Cl_2, and the extract was washed with brine, dried (Na_2SO_4) and stripped of solvent in a rotary evaporator under vacuum at 60−70 °C to give methyl *o*-toluate as a pale-yellow liquid. The yield was 52 g (94.3%, purity: 99.14%).

Method A: Ethyl 3,5-dihydroxybenzoate (Chemoselectivity). A mixture of 3,5-dihydroxybenzoic acid (5 g, 0.032 mol), diethyl carbonate (20.69 g, 0.175 mol) and conc. H_2SO_4 (0.95 g, 0.0097 mol) and acetic acid (0.58 g, 0.0093 mol) was heated under stirring at 120 °C for 3 h. Workup as above gave ethyl 3,5-dihydroxybenzoate as an off-white solid after slurrying in hexane. The yield was 5.26 g (89%, purity: 99.46%).

Method B: Dimethyl Phthalate. A mixture of phthalic acid (5 g, 0.03 mol), dimethyl carbonate (9.76 g, 0.108 mol, 3.6 equiv) and conc. H_2SO_4 (0.32 mL, 0.0058 mol) was heated under stirring at 80−85 °C for 6 h. After workup, dimethyl

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(20) (a) Kim, S.; Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, *24*, 3365. (b) Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560. (c) Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127.

(21) (a) Albertson, N. F. *Org. React.* **1962**, *12*, 157. (b) Chandrasekhar, B.; Kumar, G. B.; Mallela, S.; Bhirud, S. B. *Org. Prep. Proced. Int.* **2004**, *36*, 469.

(22) (a) Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1991**, *32*, 923. (b) Kokotos, G. *Synthesis* **1990**, 299. (c) Sugimoto, A.; Tanaka, H.; Eguchi, Y.; Ito, S.; Takashima, Y.; Ishikawa, M. *J. Med. Chem.* **1984**, *27*, 1300.

(23) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651. (a) Kiso, Y.; Kai, Y.; Yajima, H. *Chem. Pharm. Bull.* **1973**, *21*, 2507.

(24) Saito, Y.; Ouchi, H.; Takahata, H. *Tetrahedron* **2008**, *64*, 11129. in the absence of a base.

phthalate was obtained as a very pale-yellow liquid. The yield was 5.7 g (97.6% purity: 98.87%).

Method C: Methyl 4-aminobenzoate. A mixture of 4-aminobenzoic acid (5 g, 0.036 mol), dimethyl carbonate (10.95 mL, 0.131 mol, 3.64 equiv) and conc. H_2SO_4 (2.72 mL, 0.049 mol, 1.39 equiv) was refluxed for 16 h. Workup using aq $NaHCO_3$ solution (8.6 g in 86 mL water) gave solid methyl 4-aminobenzoate, mp 109−110 °C (rep 110−111 °C). The yield was 4.94 g (89.64%, purity: 99.09%).

***β*-Naphthol to 2-Methoxynaphthalane.** A mixture of *β*-naphthol (100 g, 0.694 mol), DMC (112.47 g, 1.249 mol), conc. H_2SO_4 (6.79 g, 0.0665 mol) and acetic acid (4.162 g, 0.0694 mol) was heated at 90 °C for 20 h. Excess DMC was distilled off at ∼50 °C under vacuum. Aqueous NaOH (15%, 250 mL) was added to the residue, and the mixture was stirred for 15 min; the very white solid 2-methoxynaphthalene was filtered, washed with water, and dried. The yield was 86.6 g (78.9%, purity: 99.79%), mp 69−71 °C (rep 70−73 °C).

Similarly α-naphthol gave the corresponding methy ether in 85.7% yield and 97.95% purity (2% unreacted α-naphthol).

Method D: Ethyl *p*-Hydroxybenzoate (Ethyl Paraben) (Using a Synergistic Combination of EtOH and DEC. A mixture of *p*-hydroxybenzoic acid (3 g, 0.0217 mol), diethyl carbonate (1.71 g, 0.0144 mol), EtOH (3 mL, 0.051 mol) and conc. H_2SO_4 (0.071 g, 0.000717 mol) was heated at 100 °C for 20−24 h. Usual workup gave ethyl *p*-hydroxybenzoate as a white solid, mp 113.7−115.1 °C (rep. 114−117 °C). The yield was 3.6 g (97.22%, purity: 99.46%).

Method A: Large-Scale Preparation of Methyl *m*-Toluate. Dimethyl carbonate (119.2 kg, 1.323×10^3 mol), *m*-toluic acid (100 kg, 0.7353×10^3 mol), conc. H_2SO_4 (7.2 kg, 70.5 mol) and acetic acid (4.4 kg, 73.3 mol) were charged into a 3.0 KL GLR, and the temperature was raised to 85−90 °C with steam and maintained at 85−90 °C for 12 h under stirring. TLC showed *m*-toluic acid content to be <3% w/w. The reaction mass was cooled to 25−30 °C and 10% aq $NaHCO_3$ (200 L) was added over 30 min. The aqueous mixture was stirred for 15−30 min and allowed to settle, and the aqueous and organic layers were separated. The aqueous layer was extracted once with dichloromethane (200 L) or ethyl acetate (200 L). The ethyl acetate/dichloromethane layer was separated and combined with the organic layer. The combined organic layer was washed with DM water (200 L) and then distilled in a 1.5 KL SSR first at atmospheric pressure and then under a low vacuum at ∼50 °C. Methyl *m*-toluate was obtained as a pale-yellow liquid. The yield was 107.7 kg (97.65%, purity: 98.30%).

Similarly, 260 kg of *o*-toluic acid (3.0 KL GLR) gave methyl *o*-toluate as a pale-yellow liquid. The yield was 282 kg (98.34%, purity: 99.63%).

Method A: Large-Scale Preparation of Methyl 3,5-Dimethoxybenzoate. Dimethyl carbonate (128.4 kg, 1.427×10^3 mol), 3,5-dimethoxybenzoic acid (130 kg, 0.714×10^3 mol) and conc. H_2SO_4 (14.3 kg, 0.14×10^3 mol) were charged into a 630 L GLR, and the mixture was heated to 85−90 °C with steam under stirring. The temperature was maintained for 6 h. TLC showed not more than 1% of the starting acid. The reaction mass was cooled to 25−30 °C, DM water (390 L) was added, and the mixture was stirred for 1 h at 10−15 °C. The solid obtained was centrifuged and washed with DM water (260 L). The solid was dried under vacuum at 25−30 °C until moisture content by Karl Fischer was less than 3%. The yield of methyl 3,5-dimethoxy benzoate was 138 kg (98.5%, purity: 99.54%), mp 35−39 °C (rep 31−33 °C) with a moisture content of 2.9%.

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