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Esterification of sterically hindered acids and alcohols in fluorous media

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Abstract—Sterically hindered esterification reactions are best performed in specific fluorous media in the presence of catalytic amounts of diphenylammonium triflate. Fluorous media, in addition to their positive effect on yields, have inherent favorable properties respecting environment and permitting simple work-up. Highly congested reagents, however, react only marginally.

The search for performant esterification processes is extremely active, testified by the several hundreds of articles, reviews, patents reported each year. The basic and cheapest method remains the equimolar combination of a carboxylic acid and an alcohol. The reaction is an equilibrium with constant near unity. The shift of the equilibrium in favour of the ester requires appropriate reaction conditions which consist usually in the removal of the water produced, whereas the esterification rate is accelerated in the presence of a catalyst. The difficulty is to find the right catalyst which should be as neutral as possible in order to survive to the formation of water.

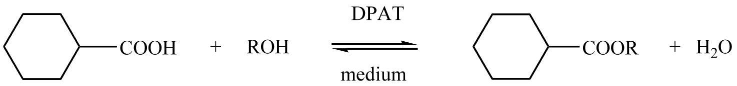
The dilemma has been described in a related note.[1] A recent esterification process took advantage of the use of a mild catalyst, diphenylammonium triflate (DPAT).[2] In this way, equimolar amounts of alcohol and acid in toluene solution could react without removal of water to form the corresponding ester in excellent yield, generally 90%, and selectivity. A recently published paper reported the condensation of both reagents in equimolar amount with hafnium and zirconium salts as catalysts under azeotropic removal of water by boiling toluene.[3] Both processes however, worked efficiently only with uncrowded alcohols and acids. Adaptation to sterically hindered systems, even moderately, failed. As we have been involved in the study of sterically demanding reactions,[4] we became interested in such esterification reactions.[5]

Initially, we checked the results of Ref. 2 by using the same catalyst (DPAT) and solvent (toluene) for a number of esterifications involving cyclohexanecarboxylic acid with various types of alcohols (Table 1, first column).[6] We chose deliberately a more crowded acid than common linear aliphatic ones. Also noteworthy, the water formed during the reaction was not removed.

The good yield obtained with *n*-octanol in toluene was in harmony with the results of Ref. 2. The more crowded 2-methyl-1-butanol gave a slighty lower yield of ester.

Table 1. DPAT-catalysed esterification of cyclohexanecarboxylic acid (DPAT 2% mol, 80°C, 8 h, acid:alcohol = 1:1.1, with stirring)

R	Yield (%)	
	Toluene	FC-77®
n-Octyl	84	64
Et(Me)CH-CH_2	70	81
t-BuCH_2 (neopentyl)	13	27
i-Pr	12	22



Keywords: esterification; fluorophobic medium; steric hindrance.

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However, the results concerning the sterically congested neopentanol and the secondary alcohol, 2-propanol, were much less satisfactory. In our search for pressure multiactivation of sterically hindered reactions,[4,5] we have been interested in combining solvophobic activation,[7] lastly fluorophobic activation.[8] This prompted us to study the effect of perfluorohydrocarbons as the medium in our esterification reactions. A literature screening showed the advantage of using such media in a number of organic reactions.[9]

The same reactions depicted in Table 1 were, therefore, carried out in the commercially available FC-77®, a liquid consisting of a mixture of perfluoroalkanes and perfluorocyclic ethers (column 2 in Table 1). While the yield of *n*-octyl ester was decreased, those obtained in the fluorous medium were higher in the runs with branched alcohols, particularly in the reaction involving the hindered alcohols, neopentanol and isopropanol (Table 1). In fact, the ester yield resulted from a subtle compromise between esterification and hydrolysis. Under kinetic conditions, the equilibrium reached its maximum at 80°C after 20–24 h when reagents with hindered structures were reacted. As an example, in the esterification of cyclohexanecarboxylic acid with neopentanol and 2-propanol, respectively, the yields were in the order of 85 and 65% in another fluorous medium (perfluorohexane) whereas the maximum yields in toluene were only 50 and 15–20%, respectively.

Table 2. Temperature effect in the DPAT-catalysed esterification of 2-propanol with cyclohexanecarboxylic acid in FC-77® (DPAT 2% mol, 24 h)

Temp. (°C)	45	60	80	95
Yield (%)	20	37	52	54

Inspired by these results we extended the method to encumbered systems involving neopentanol and secondary alcohols opposed to structurally hindered or aromatic acids (Table 3). A temperature study showed that the optimal temperature was 80°C (Table 2).

The following comments are in order:

(i) The esterifications listed in Table 3 proceeded with more or less difficulty yielding the corresponding esters in variable yields from 0 to 84%.

(ii) In every case fluorous media proved to be superior to toluene, tetradecafluorohexane being generally more efficient than FC-77®. Whereas the yields in the three investigated media were comparable with less sterically hindered substrates (entries 5, 8, 10, and 17), operation in C_6F_{14} was straightforward with increasing complexity of both acid and alcohol (entries 1, 2, 4, 9, 11, 12, 13, 14, 16). Tertiary alcohols did not react.

(iii) Although most reactions were carried out with 10% mol DPAT, the concentration of the catalyst had minor importance. The yield remained almost unchanged when the concentration was increased from 2 to 5 and 10% mol (entries 2 and 3).

Table 3. DPAT-catalysed esterifications in fluorous media (80°C, 24 h, acid:alcohol = 1:1.1, all reactions except two[b] were performed under stirring) (nr, no run)

Entry	Acid	Alcohol	DPAT (% mol)	Yield (%)		
				C_6F_{14}	FC-77®	Toluene
1	Cyclohexanecarboxylic	Neopentanol	10	84	65	50
2	d°	2-Propanol	2	65	52	15
	d°	d°	2	49[b]		
	d°	d°	5	67	nr	nr
	d°	d°	I_2 (10%)[a]	31	nr	nr
3	d°	2-Butanol	2	66	58	41
	d°	d°	2	58[b]		
	d°	d°	5	68	56	nr
	d°	d°	10	65	57	nr
4	d°	2-Pentanol	2	58	47	25
5	d°	Cyclohexanol	2	54	55	43
6	d°	*t*-Butanol	10	0	nr	0
7	Benzoic	Neopentanol	10	70	60	49
8	d°	2-Butanol	10	25	nr	21
9	*p*-Toluic acid	Neopentanol	5	52	nr	25
10	Isobutyric	Cyclohexanol	10	65	nr	57
11	d°	Neopentanol	10	48	22	10
12	*t*-Butylacetic	Neopentanol	10	77	45	34
13	d°	2-Butanol	10	20	nr	7
14	Pivalic	Neopentanol	10	nr	42	7
15	d°	2-Propanol	10	Low	nr	0
16	d°	2-Butanol	10	11	9	5
17	Tetrahydro-2-furoic	Neopentanol	10	69	nr	61

[a] See comment (iv).

[b] Without stirring (see comment (vi)).

Table 4. Effect of the medium in DPAT-catalysed esterifications (80°C, 24 h, DPAT 2% mol)

Acid	Alcohol	Yield (%)			
		C_6F_{14}	FC-77®	DFP[a]	*n*-Hexane
Cyclohexanecarboxylic	2-Propanol	65	52	31	19
d°	Neopentanol	84	65	59	40
Isobutyric	d°	48	22	28	12

[a] 1,1,1,2,3,4,4,5,5,5-Decafluoropentane

(iv) In place of DPAT, we used iodine which was recommended as an efficient catalyst for esterifications (entry 2).[10] The original method used the alcohol as the medium. In C_6F_{14} the yield of ester was much lower than in the presence of DPAT.

(v) In our temperature conditions, all reagents were liquid except benzoic acid. In order to solubilise this acid a small amount of either toluene or chloroform (3.5 mmol) was added, before dilution with C_6F_{14} (entry 8). The yield was lowered (16%). This may be in relation with the paragraph below.

(i) As the fluorous reactional system was heterogeneous, stirring was preferred (compare the yields of ester obtained in C_6F_{14} in entries 2 and 3).

The results of Table 3 may be rationalised in the following way. DPAT remains in the organic phase containing the reagents since the blue-green colour developed during reaction is only visible in this layer. Reaction occurs, therefore, mainly at the interface between the fluorous medium and the organic phase. The results obtained with unhindered alcohols and acids (comparable yields in toluene and fluorous media) could be explained by a partial miscibility of water with the acid and/or alcohol. Hindered reagents are less miscible impeding hydrolysis to some extent. The role of the fluorous phase is certainly determining in separating the water produced. In runs carried out with hindered structures a three-phase system exists (fluorous medium–water–reagents). Whether the increase in reactivity under such conditions may be ascribed to fluorophobic interactions[11] should be taken into account. To verify this possibility, esterifications were performed in *n*-hexane which is also a non-polar immiscible medium of similar dielectric constant and cohesive energy density (Table 4). The yields were decidedly lower in hexane compared to fluorous media. This could be an indication of the operation of fluorophobic activation. If this is true, solvophobic interactions should be highest in perfluorohexane. The partially fluorinated compound DFP is less efficient probably owing to the two hydrogen atoms, reducing solvophobicity.

Conclusion

In conclusion, esterification of bulky acids and alcohols are best performed in fluorous media, particularly perfluorohexane, in the presence of the mild and cheap catalyst, diphenylammonium triflate. The yield of ester, however, is very variable. The advantage of using fluorous hydrocarbons, in addition to enhancing reactivity, materialises in their environmental innocuity, full recovery by simply extracting the ester layer and re-use in subsequent runs. Other fluorous compounds with higher boiling points can also serve as media provided that they have non-amphiphilic properties. In summary, the present esterification process involving hindered reagents is revealed as a cheap and the most performant method to date. However, in order to acquire its full potentiality, the yields must still be improved.

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6. *Typical experimental procedure*: A mixture of DPAT (20 mg, 0.31 mmol), cyclohexane carboxylic acid (400 mg, 3.12 mmol), bibenzyl (standard) (about 50 mg), and alcohol (3.43 mmol) were placed in a 6 mL flat-bottomed stainless steel autoclave equipped with a magnet. The volume was adjusted with the solvent. The cell was closed, placed on a magnetic stirrer and heated to 80°C for 24 h. After reaction, the autoclave was cooled down before opening and the bilayered liquid system (when hexane or fluorous media were used) was poured into a separatory funnel. The blue upper organic layer was separated from the fluorous compound which was kept for re-use. After evaporation of the volatile compounds, the residue was analyzed by ^1H NMR and the yields determined from relative intensities of characteristic protons of the ester versus methylene groups of the internal standard.
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