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Research Article

Novel solvent-free labelling procedure with carbon-14 diethyl malonate

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Summary

A rapid and novel one-pot radiochemical synthesis of ^{14}C-labelled esters has been developed using a combination of solvent-free conditions and microwave irradiation. The method offers several advantages over the customary classical procedure. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: microwave irradiation; solvent-free synthesis; malonic alkylation; carbon-14 labelling

Introduction

Despite the developments achieved in tritium-labelled compounds characterization by the introduction of ^{3}H NMR spectroscopy, carbon-14 labelled compounds are the most frequently used radiochemicals in drug pharmacokinetics and metabolic studies. It is known, moreover, that the synthesis of complex molecules using carbon-14 organic precursors is in general a multistep and time-consuming procedure involving tedious purification and isolation of the final product. The development of alternative synthetic techniques to

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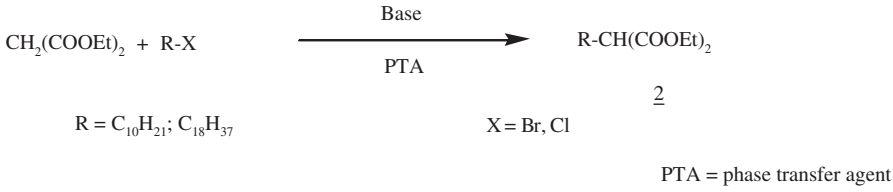
improve the efficiency of radiochemical preparation is strategically important in order to search for new potential pharmaceuticals. In this regard, the advantages[1] brought by synthesis under solvent-free conditions as 'green chemistry' procedures are especially attractive. Mild reaction conditions, easy purification, improved waste management and kinetic enhancements achieved in preparations using this technique in combination with microwave activation[2] are of considerable benefit also for short half-life isotope radiochemistry.[3,4]

In this work, solvent-free synthesis using solid–liquid phase transfer catalysis (PTC) conditions for carbon-14 labelling with diethyl malonate is described. This leads to a novel one-pot procedure for ester preparations involving diethyl malonate alkylation followed by dealkoxycarbonylation.

Results

The main disadvantages of carrying out malonic alkylation by classical routes lie in the long reaction times and the tedious product purification due to the use of DMF as a solvent. Under solvent-free conditions, the yields of diethyl malonate alkylation in the presence of catalytic amounts of PTC (Scheme 1) depend strongly on a number of parameters, in particular on the efficiency of carbanion formation achieved by a base and its subsequent phase transfer by a catalyst in liquid alkyl halides (acting here both as electrophile and organic phase).

Previous results obtained with related anionic-mediated reactions (the alkylation of β-ketoesters)[5] under solvent-free conditions, when coupled to microwave activation (MW), lead to excellent yields when a strong solid base as KO*t*Bu and quaternary ammonium salts such as Aliquat 336 were used as phase transfer agent (PTA). The same system was also successfully used in the monoalkylation of diethyl malonate. Acceptable yields were achieved within 10 min at 130°C (Table 1).



Scheme 1.

Table 1. Solvent-free PTC alkylation of diethyl malonate with *n*-bromooctadecane (1.5 eq.) using microwaves (130°C, 10 min; PTA = Aliquat 336; base = KO*t*Bu). Influence of temperature and reaction time

t (min)	*T* (°C)[a]	%2[b]	%RBr[c]
5	90	66	8
10	130	74(67)	9
10	130	70[d]	–
10	160	72	7

[a] Temperature measured by IR detection under microwave irradiation.
[b] gc yields using an internal standard (dioctylphthalate) and yield of isolated product in brackets.
[c] Remaining alkyl bromide.
[d] 2 equiv. of RBr.

Table 2. Solvent-free PTC alkylation of diethyl malonate with *n*-bromooctadecane using microwaves (130°C, 10 min; PTA = Aliquat 336). Influence of the base on yield (%2)

KO*t*Bu	EtONa	KF/Al_2O_3	K_2CO_3
74	0	6	13

Similar monoalkylation yields were obtained when there was a scaling-up of the reaction from 2 to 10 mmol, thereby illustrating the attractions of carrying out malonic alkylation under solvent-free conditions.

The only trace impurities formed, as detected by gc/ms, are the dialkylated products. When weaker bases were employed, the reaction with *n*-bromooctadecane hardly takes place at all (Table 2). The best yields were obtained using potassium *t*-butoxide. The successful microwave irradiated alkylation of diethyl malonate with K_2CO_3/TBAB reported in a domestic oven[6] seems to be limited to the case of more reactive alkyl halides such as *n*- butyl, *n*-propyl, allyl and benzyl bromides or chlorides.

The results obtained when the reaction was carried out in the absence of PTA clearly display a noticeable difference in yields when compared with reactions performed in their presence (Table 3). Conversely, alkylation yields are not significantly affected by changing the nature of the tetraalkylammonium salts.

Alkylation under the same reaction conditions, using a lower molecular weight alkyl bromide such as *n*-decyl bromide, leads to similar yields of monoalkylated product (Table 4). Respective reactions, when using alkyl chlorides, display a dramatic decrease in yields, which

Table 3. Solvent-free PTC alkylation of diethyl malonate with *n*-bromooctadecane using microwaves (130°C, 10 min; base = KO*t*Bu). Influence of the catalyst on yield (%2)

Without PTA	Aliquat 336	NBu_4Br	TEBA,Cl	NBu_4HSO_4
21	74	74	69	75

Table 4. Solvent-free PTC alkylation of diethyl malonate with *n*-alkyl halides ($n = 10, 18$). Leaving group effect (base = KO*t*Bu; PTA = Aliquat 336). Influence of activation mode on yield (%2)

	X = Br ($t = 2$ min)		X = Cl ($t = 10$ min)	
	Activation mode, (%) 2		Activation mode, (%) 2	
R	MW[a]	Δ[b]	MW	Δ
n-$C_{10}H_{21}$	69	60	20	21
n-$C_{18}H_{37}$	65	62	23	20

[a] MW = microwave activation.
[b] Δ = conventional heating using thermostated oil bath under a similar set of conditions.

reached only 3% for the larger (octadecyl) alkyl radical. The observed leaving group effect, which is not affected by microwave irradiation, implies the need to use brominated electrophiles due to the lower bond energy (C–Br : 297, C–Cl : 356 kJ/mol).

Compared to the classical preparation in DMF, solvent-free synthesis with diethyl malonate in the presence of Aliquat 336 is particularly advantageous in terms of greatly reduced reaction time and favourable experimental details e.g. with *n*-bromooctadecane.

Solvent-free/PTC	KO*t*Bu, Aliquat 336	74% of 2
(oil bath or microwave activation)	130°C, 10 min	
Classical synthesis	NaH, DMF, 100°C, 12 h	69% of 2

No dilution by solvent provides optimal concentrations of reactant and enhancement in reaction kinetics. Although the chemical yields remain approximately the same at about 70%, solvent-free reaction with catalytic amount of PTA is 60 times faster than the classical reaction, while purification is greatly simplified. The absence of DMF is a further attractive feature. In the absence of any added organic solvent, the electrophile acts both as reagent and as organic phase and provides the liquid phase in which the reaction takes place. An excess of RBr

allows not only desirable conditions for radiochemical preparation, but also provides for easier work-up and simpler microscale radiolabelling. The halide excess can be easily removed from the reaction mixture by elution with an apolar solvent (petroleum ether, *n*-hexane).

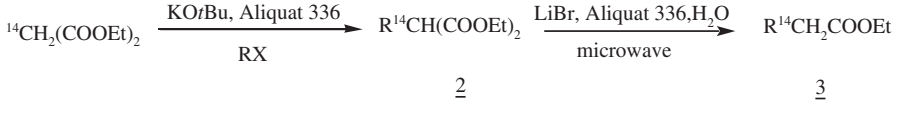
Contrary to previous reports of using other anionic species[7] under solvent-free catalytic conditions, we have not observed any difference between microwave activation and classical heating. The specific microwave effect was assumed to be connected to an increase in polarity of a system as the reaction progresses. It could be important when mechanisms imply a more polar transition state (TS) compared to the ground state (GS) of the reactions[8]. In the present case, the modification in polarity between GS and TS is very small; negative charge delocalization in the malonate ion will lead to very loose ion pairs.

The established reaction conditions, when applied to the preparation of 2-^{14}C octadecyl malonate, confirmed the advantages of the proposed method for radiochemical preparations. The radiochemical yield of labelled compound after its isolation by preparative flash chromatography was 67% and the radiochemical purity as determined by radio tlc reached 95%.

Fatty ester preparation

In order to develop a procedure for fatty ester preparation that could lead to a fast (carbon-14 and tritium) labelling method, a one-pot synthesis based on the above-discussed solvent-free malonic alkylation, followed by microwave-activated dealkoxycarbonylation (Krapcho reaction), (Scheme 2) was performed.

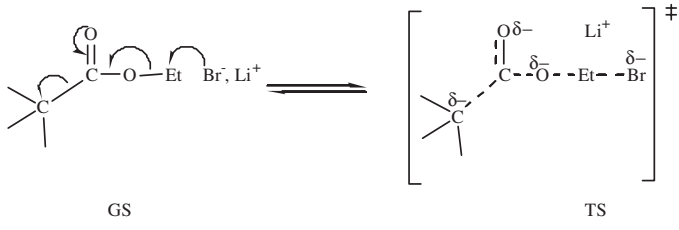
By means of a simple procedure with no need for the isolation of the intermediate, acceptable yields of esters (57–60%) were achieved within 12–20 min (Table 5). A remarkable influence of specific (non-purely thermal) microwave activation to enhancement in ester yield is observed. This is in agreement with the microwave effect reported for



Scheme 2.

Table 5. One-pot ester preparation with *n*-alkyl halides ($n = 10, 18$). Influence of activation mode on yield (%3)

KO*t*Bu/ Aliquat 336 $LiBr + H_2O$		Activation mode			
		Δ		MW	
R	*t* (min)	(%)2	(%)3	(%)2	(%)3
$C_{10}H_{21}$	2 + 10	19	39	5	60
$C_{18}H_{37}$	10 + 10	18	32	8	57



Scheme 3.

other related Krapcho reactions[7] under similar catalysis conditions. In this case, the polarity increases from GS to TS as a result of negative charge delocalization. These considerations are consistent with the observed specific microwave effect (Scheme 3).

When compared to the 45% overall yield of fatty ester achieved by the same two- step synthesis under classical conditions, the solvent-free approach is considerably faster and easier to accomplish. The established reaction conditions are conducive to simple ^{3}H and ^{14}C isotopic labelling of high molecular weight esters. By using microwave cavities of special design dedicated to PET radiopharmaceutical production[9], an alternative[10] solvent-free, rapid and easily automated production of 2-^{11}C fatty esters could be developed.

Experimental

General

For the sake of comparison, all reactions under microwave irradiation and classical heating (oil bath) were performed under the same conditions of time, temperature and amount of reactants. The microwave reactor was a monomode system (Synthewave^{TM} 402-

Prolabo) with focused waves operating at 2.45 GHz, specially designed for organic synthesis with an accurate control of temperature by IR detection and mechanical stirring with adjustable rotation speed. All reactions were performed in an open vessel. Chemical yields were evaluated by gc using an internal standard, e.g. octylbenzoate or dioctylphthalate.

Flash column chromatography was performed using 35–70 μm silica gel 60 (purchased from SDS). Analytical tlc were obtained using Merck silica gel 60 precoated on aluminium sheets and analytical gc were performed on a Fisons 9000 series apparatus, fitted with a column CP Sil 5CB, 25 m (temperature program: 150–250°C, and 200–280°C at 10°C/min, respectively, for *n*-decyl and *n*-octadecyl bromides).

2-^{14}C-diethyl malonate (56.7 mCi/mmol) was supplied by Izotope Ltd (Budapest Hungary). The desired specific activity was obtained by dilution of the commercial high specific activity malonate. Reaction with labelled diethyl malonate was performed in a 10 ml, two-neck round-bottom flask attached to a carbon-14 labelling line.

Labelling procedure

To a mixture of 2 mmol of 2-^{14}C diethyl malonate (0.5 mCi/mmol) and 5% of Aliquat 336 (0.1 mmol) potassium *t*-butoxide (2 mmoles, 1 eq.) is added under magnetic stirring in order to generate the carbanion. Alkyl halide (2 mmol, 1 eq.), previously melted in the case of *n*-bromooctadecane, is then added slowly. The flask is left whilst stirring for 10 min inside an oil bath at 130°C. After cooling, the mixture is diluted with ethyl acetate (20 ml) and filtered on Florisil (1 g). After evaporation, pure labelled ester is isolated by flash chromatography (petroleum ether:ethyl acetate/35:1). The product fraction is tested for radiochemical purity by tlc in benzene, recording the radiochromatogram by using a Berthold Radioscanners' ionization camera. Liquid scintillation counting (LSC) was done using a Rackbeta 209 Spectrometer. The radiochemical yield was then evaluated from the radioactivity.

One-pot preparation

To a mixture of diethyl malonate (2 mmol) and 5% of Aliquat 336 (0.1 mmol) potassium *t*-butoxide (2 mmoles, 1 eq.) is added under magnetic stirring for 5 min. Alkyl halide (2 mmoles, 1 eq.) is then slowly added. The flask is left whilst stirring for 10 min inside an oil bath at

130°C. After cooling, 4 mmoles (2 eq.) of LiBr and 4 mmoles (2 eq.) of water were added and the mixture was irradiated with microwaves for 10 min at 200°C. After cooling, the mixture is diluted with ethyl acetate (20 ml) and filtered on Florisil (1 g). After evaporation, purification is carried out by flash chromatography using petroleum ether:ethyl acetate (35:1) as a mobile phase.

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