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Benzylation of 1,3-diketons in the phase transfer catalysis condition by microwave irradiation

Abstract

The alkylation of ethyl acetoacetate and diethyl malonate with benzyl chloride by microwave radiation in phase transfer catalysis conditions is investigated in comparison of studied technique of alkylation with the usual method in the same phase transfer catalysis conditions. As the catalyst quaternary ammonium salt–triethylbenzylammonium chloride (TEBAC) has been used. It is shown that the conduct of the phase transfer catalysis benzylation in combination with microwave radiation contributes to monobenzylation of the studied 1,3-diketone derivatives.

Keywords: phase transfer catalysis, microwave radiation, ethyl acetoacetate, diethyl malonate, benzyl chloride, triethylbenzylammonium chloride, benzylation

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Abbreviations: EAA, ethyl acetoacetate; DEM, diethyl malonate; TEBAC, triethylbenzylammonium chloride; PTC, phase transfer catalysis; BzCl, benzyl chloride

Introduction

1,3-diketones as ethyl acetoacetate (EAA) and diethyl malonate (DEM) are widely used to obtain a wide range of highly effective excipients in fine organic synthesis, specially for pharmaceutical industry. Microwave (MW) radiation exposure can significantly speed up reactions and increase the exit of the targeted materials, reducing the resorption in organic synthesis. MW radiation is a crucial tool for the development of green chemistry. Advantages of this method are - lack of heat, cleanliness of the reaction, practical instantaneous heating of the reaction mass to the given temperature and, in particular, replacing the traditional solvent with an elevated and polar solvent.[1,2] In this presentation have comprised the studied technique of alkylation in the usual phase transfer catalysis (PTC) in the same PTC condition with the combination of MW technique for the choice more convenient conditions for this important product synthesis. It is had been known, that the combination of the MW–PTC techniques was used in the alkylation of active methylene containing substrates such as ethyl acetoacetate.[3]

Results and discussion

Previously it has been shown that the EAA (DEM) alkylation causing mono- and dialkylated products.[4] In this study, the EAA (I) and DEM (II) alkylation were studied under the PTC conditions with MW and the results were compared with those carried out under ordinary PTC conditions. It is known that the MW promotes rapid and adequate warming of the reaction medium as well as activates the molecules by generating ions and radicals.[1,2] In an aqueues alkiline PTC system, under the conditions of radiation exposure the hydrolisis of ether bonds obtained only with formation of ethyl alcohol.

From the Table 1 it follows that the combination of MW radiation with the PTC system "solid phase-liquid" promotes highly selective benzylation of the EAA and DEM by BzCl with the formation of the product of monobenzylation. The same process in PTC "liquid-liquid" system with MW radiation passes with the hydrolysis of the ester group of the 1,3-diketones. By the way, when the products were isolated from benzylation of AEE a floral-herbaceous odor specific for benzyl acetone was felt. The data from the Table 1 suggests that the combination of the MW radiation contributes to the PTC "solid-liquid" system with high selectivity mono-benzylated product of 1,3-diketones formation.

Experimental part

MW radiation was carried out in a domestic MW oven "Electronika SP-23 ZIL" (Russia), frequency - 2450 MHz. The oven was equipped with a rectangular waveguide. The liquid chromatography was performed with a Shimadzu-Japan apparatus equipped with a diodomatrix detector, NUCLEOSIL 100-5 with a column, C18 size 150x4, 6mm, diameter of particles of sorbent 5microns, mark Macherey-Nagel Liquefaction is carried out by an isocratic regime. The isolated products are identified by IRS (Specord IR-75) and NMR (Varian "mercury-300" RS) methods. The chemical shifts are expressed by ppm with respect to $Si(CH_3)_4$, solvent was $CDCl_3$. The mass spectra were recorded on a MX-1320 device using direct injection of the sample into the ionic source, the ionization temperature of the camera was 60°C and the energy of ionizing was 65EV. Alkylation of EAA (DEM) with benzyl chloride (BzCl) was carried out at a molar ratio of EAA (DEM): BzCl: 10N aqueous potassium hydroxide solution: TEBAC=1: 1.2:2:0.1. The reaction mixture was heated by thermal and MW radiation. The identification of the products obtained was carried out by a number of physical constants and by liquid chromatography with previously obtained compounds (Figure 1).

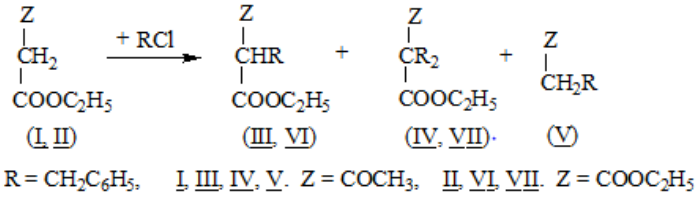

Figure 1 Alkylation of EAA (I) and DEM (II) with BzCl in the PTC.

Benzylation of EAA in PTC "liquid-liquid" system

In a three-necked flask equipped with a reflux condenser, mechanical stirrer and a drop wise container, placing 13.0g (0.1mol) EAA, 15.18g (0.12mol) BzCl, 2.28 g (0.01mol) of TEBAC. When heated in a boiling water bath and intensive stirring to a mixture of 20ml 10N (0.2mol) aqueous solution of KOH was added over a period of 20minutes. After that, the heating was continued for another 20minutes. The reaction mixture was extracted with diethyl ether, the ether extract was dried over sodium sulfate, the ether was distilled off and the residue was distilled in vacuo. It was obtained 3.55g of benzyl acetone (V) with b.p. 98-99°C (5mm Hg), nD201.5120, 6.16g ethyl benzylacetoacetate (III) with b.p. 110-112°C (2mm Hg), nD201.5030,[4] 8.06g ethyl dibenzylacetoacetate (IV) with b.p. 150-155°C (1mm Hg), nD201.5251.[4] The results are given in the Table 1 & Table 2.

Table 1 1,3-diketone benzylation in PTC

1,3-diketone	Potassium hydroxide	The reaction products (yield, %)	
		by usual heating*	by MW radiation**
EAA	10 N KOH aqueous solution	III (28), IV (26), V (24),	Hydrolysis
DEM		VI (51), VII (trace),	Hydrolysis
EAA	KOH dry powder	III (20), IV (46), V (18),	III (60), V (trace)
DEM		VI (62),	VI (67), VII (18)

*) at 40min, in 85-87°C

**) at 10min, in 60-80°C

Table 2 Physical-chemical data of synthesized compounds

Sr. No.	Compound	B.p. °/mm	n_D^{20}	IR, ν, sm $^{-1}$	NMR, NMR, ^{1}H, δ, m.p.	MS, m/z
1.	$CH_3C(=O)CH_2CH_2C_6H_5$ **Y**	98-99/5	1,5120	740, 1130, 1580, 1600, 3030.3080 (C_6H_5); 1720 (C=O).	1,22s (3H); 1,75t (2H, C$\underline{H}_2$); 2,72m (2H); 7,13÷7,27m (5H, $C_6\underline{H}_5$);	-
2.	$CH_3C(=O)CH(CH_2C_6H_5)C(=O)OCH_2CH_3$ **III**	110-112/2	1,5030	1710 (C=O). 1740 (C=O-OCH_2CH_3)	1,3 (3H,$OCH_2C\underline{H}_3$); 2,56m (2H, $CH_2C\underline{H}_3$); 3,12m (2H, $OCH_2C\underline{H}_3$); 4,31m(1H, C$\underline{H}CH_2$); 7,25m (5H, $C_6\underline{H}_5$);	-
3.	$CH_3C(=O)C(=O)C(=O)OCH_2CH_3$ $(CH_2C_6H_5)_2$ $CH_3C(=O)C(=O)C(=O)OCH_2CH_3$ $(CH_2C_6H_5)_2$ **IY**	150-155/1	1,5251	1720 (C=O). 1750(C=O-OCH_2CH_3)	1,37c (3H, C$\underline{H}_3$); 2,68c (4H, (CH_2)); 3,21м (2H,$OC\underline{H}_2C\underline{H}_3$); 7,30м (10H, $2C_6\underline{H}_5$);	43, 45, 77, 177, 179, 205, 220, 310
4.	$CH_3CH_2OC(=O)CH(CH_2C_6H_5)C(=O)OCH_2CH_3$ **VI**	160-162/10	1,4858	1760, 1735(C=O)	1,15t(6H, $2C\underline{H}_3$); 2,41d (2H,$C\underline{H}_2C_6\underline{H}_5$); 3,15-3,25 t (1H, $CH_2C_6\underline{H}_5$); 7,25-7,37 (5H, $C_6\underline{H}_5$);	
5.	$CH_3CH_2OC(=O)C(=O)C(=O)OCH_2CH_3$ $(CH_2C_6H_5)_2$ $CH_3CH_2OC(=O)C(=O)C(=O)OCH_2CH_3$ $(CH_2C_6H_5)_2$ **VII**	viscous loquid	-	-	-	44, 77, 135, 226,282, 311, 340

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Benzylation of DEM in PTC "liquid-liquid" system

This reaction carried out similarly for benzylaton of EAA, with 16.0g (0.1mol) DEM, 15.18g (0.12mol) BzCl, 2.28g (0.01mol) of TEBAC. It was obtained 12,5g diethyl benzylmalonate (VI) with b.p. 160-162°C (10mm Hg), nD201.4858.[4] The results are given in the Table 1 & Table 2.

Benzylation in PTC "solid-liquid" system

13.0g (0.1mol) of EAA (or 16.0g (0.1mol) of DEM), 15.18g (0.12mol) of BzCl, 2.28g (0.01mol) of TEBAC are placed in a flask equipped with a reflux condenser and mechanical stirrer, 11.2g (0.2mol) of dry powder-like KOH. The mixture was vigorously stirred in a boiling water bath for 40minutes. The reaction mixture was extracted with diethyl ether, the ether extract was dried over sodium sulfate, the ether was distilled off and the residue was distilled in vacuo (Tables 1) (Table 2).

Benzylation in PTC "liquid-liquid" system with MW radiation

A flask with a mixture of 13.0g (0.1mol) of EAA, 15.18g (0.12mol) of BzCl, 2.28g (0.01mol) of TEBAC, 20ml 10N (0.2mol) aqueous solution of KOH was placed in a MW oven. The process continued for 10minutes. The reaction mixture was extracted with diethyl ether, the ether extract was dried over sodium sulfate, and the ether was distilled from the ether solution. The reaction products were investigated by liquid chromatography. The reaction process was characterized on the basis of the amount of ethyl alcohol detected (Tables 1) (Table 2).

Benzylation in PTC "solid-liquid" system with MW radiation

A flask with a mixture of 13.0g (0.1mol) of EAA, 15.18g (0.12mol) of BzCl, 2.28g (0.01mol) of TEBAC, 11.2g (0.2mol) of dry powder of KOH was placed in a MW oven. The process continues for 10minutes. The reaction mixture was extracted with diethyl ether, the ether extract was dried over sodium sulfate, and ether was distilled from the ether solution. The reaction products were examined by liquid chromatography (Tables 1) (Table 2).

Conclusion

It has been established the possibility of selective synthesis of monobenzylated products by the benzylation of 1,3-diketones with benzyl chloride under the combination of the MW–PTC techniques. It has been shown that the reaction with 10 N KOH aqueous solution as base leads to the 1,3-diketones hydrolysis product formation (ethanol) under the same combination.

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None.

Conflict of interest

Author declares that there is no conflict of interest.

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