Acylation of a substituted benzofuran over an HY zeolite and its subsequent deacylation and reacylation

Patricia Amouzegh, Annie Finiels, Patrick Geneste, Erick Ginestar and Patrice Moreau

Laboratoire des Matériaux Catalytiques et Catalyse en Chimie Organique, URA CNRS 418, Ecole Nationale Supérieure de Chimie, 8 rue de l'Ecole Normale, 34053 Montpellier Cedex 1, France

Received 13 February 1995; accepted 16 June 1995

The acylation reaction of 2-butylbenzofuran with *p*-anisoyl chloride and *p*-anisic acid in the presence of faujasite type zeolites, in the liquid phase, is reported. A good initial selectivity to the 3-acylated derivative is obtained, but the selectivity decreases with time. This result is explained by the involvement of a deacylation–reacylation process.

Keywords: benzofuran; acylation reaction; HY zeolites; liquid phase; 4-methoxybenzoic acid

1. Introduction

The first step of the synthesis of amiodarone, the active principle of cordarone (a drug with antidisrythmic properties), involves the acylation of 2-butylbenzofuran with *p*-anisoyl chloride, yielding 2-butyl-3-(4-methoxybenzoyl)benzofuran. This reaction is generally carried out in the presence of Lewis acids, mainly ferric aluminum or tin^{IV} chlorides, as catalysts [1,2]. It is known that such catalysts lead specifically to the acylation at the 3-position of the 2-alkylbenzofurans [1]. Nevertheless, their industrial use leads nowadays to more and more concern for the environment, so that their replacement by solid acid catalysts is obvious [3]. Besides their well-known shape-selective and acidic properties and their thermal stability, zeolites meet the essential requirements for industrial processing of organic chemicals taking into account their environmental advantages [4]. A number of organic reactions over zeolites has now been described [5], and, in our group, aromatic electrophilic substitution reactions, such as acylation [6,7] and alkylation [8,9], have been especially developed over various zeolites under liquid-phase conditions. More recently, it has been shown that dealuminated HY zeolites were also efficient catalysts for the acylation reaction of hetero-aromatic derivatives, such as thiophene [10] or benzofuran [11], in the liquid phase.

© J.C. Baltzer AG, Science Publishers

This paper deals with the acylation of 2-butylbenzofuran with *p*-anisoyl chloride and *p*-anisic acid in the presence of faujasite type zeolites, in the liquid phase.

2. Experimental

Chemicals. 2-butylbenzofuran (97%), *p*-anisoyl chloride (99%), *p*-anisic acid (99%) and the solvent 1,2-dichlorobenzene (99%) (Aldrich Chemical) are used as supplied.

Catalysts. The HY zeolite (Si/Al = 15) is from ZEOCAT, Montoir de Bretagne (ZF 515). The typical composition is: SiO_2 94.5, Al_2O_3 5.4, Na_2O 0.1 (wt%), BET surface area: 800 $m^2\ g^{-1}$.

Procedure. The reaction is carried out in a glass reactor equipped with a magnetic stirrer and heated in an oil bath. The standard procedure is the following: the catalyst (0.5 g freshly calcined at 400°C) is added, at room temperature, to the 2-butylbenzofuran (5 mmol) in 50 ml 1,2-dichlorobenzene, and the mixture is stirred; the acylating agent (15 mmol) is then added and the mixture is heated to reflux (180°C). Samples are withdrawn periodically and analysed by gas chromatography (OV1 capillary column, length 15 m) or/and by HPLC (Kromasil RP C18 5 mm column, length 15 cm, elution: CH_3CN/H_2O 65/35, detection: UV 254 nm).

Identification. The 2-butyl-3-anisoylbenzofuran is identified by comparing its retention time to that of a commercial sample provided by SANOFI, as well as by mass spectrometry and ^{13}C NMR, after separation from the reaction mixture by chromatography (SiO_2 column, eluent: hexane–ether). The 2-butyl-6-anisoylbenzofuran is also identified by mass spectrometry and ^{13}C NMR after separation; the minor component cannot be separated.

3. Results and discussion

The acylation reaction of 2-butylbenzofuran **1** was investigated over HY zeolites (mainly HY with a Si/Al ratio of 15) as catalysts, using *p*-anisoyl chloride and *p*-anisic acid as acylating agent, at the reflux temperature (180°C) of the solvent 1,2-dichlorobenzene. The main product of the reaction is the desired 3-acylated derivative **2**, the 2-butyl-3-(4-methoxybenzoyl)benzofuran (more commonly called 2-butyl-3-anisoyl benzofuran). The evolution of the reaction (disappearance of **1** and formation of **2**) is shown in figs. 1 and 2.

A consideration of these figures leads to the following remarks:

– Although the interest to substitute *p*-anisic acid for *p*-anisoyl chloride is obvious, taking into account the inconvenience of the use of acyl chlorides because of the evolution of HCl during the reaction, the results show that, when *p*-anisic acid is used, the initial rate of the acylation reaction is much lower (v_0: 0.2 mmol ℓ^{-1} min^{-1}) than in the case of the chloride (v_0: 2.8 mmol ℓ^{-1} min^{-1}).

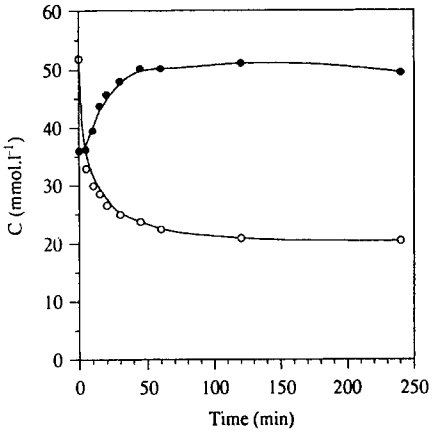


Fig. 1. Acylation of 2-butylbenzofuran with *p*-anisoyl chloride: disappearance of **1** (○) and formation of **2** (●) versus reaction time in minutes.

– In both cases, a reasonably good selectivity in the 2-butyl-3-anisoyl benzofuran **2**, is obtained.

Two other isomers are formed; the major one was identified as the 2-butyl-6-(4-methoxybenzoyl)benzofuran (more commonly 2-butyl-6-anisoyl benzofuran) **3**; the minor component, which cannot be separated, gives a mass spectrum which does not permit to identify clearly the position of the methoxybenzoyl group. Taking into account the reactivity of the aromatic ring in the benzofuran series [12], it is assumed that this minor component is the isomer acylated at the position 4 (scheme 1).

The initial formation of the three acylated isomers is explained by a parallel electrophilic attack of the acylium ion $ArCO^+$ on the furan ring (3-position) and on

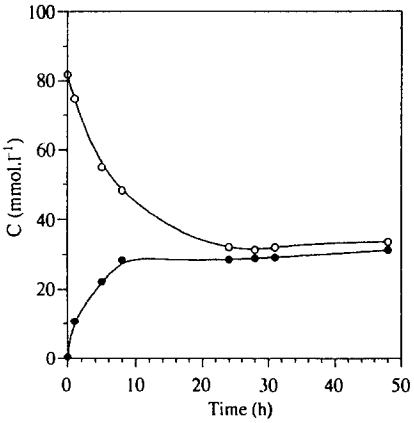
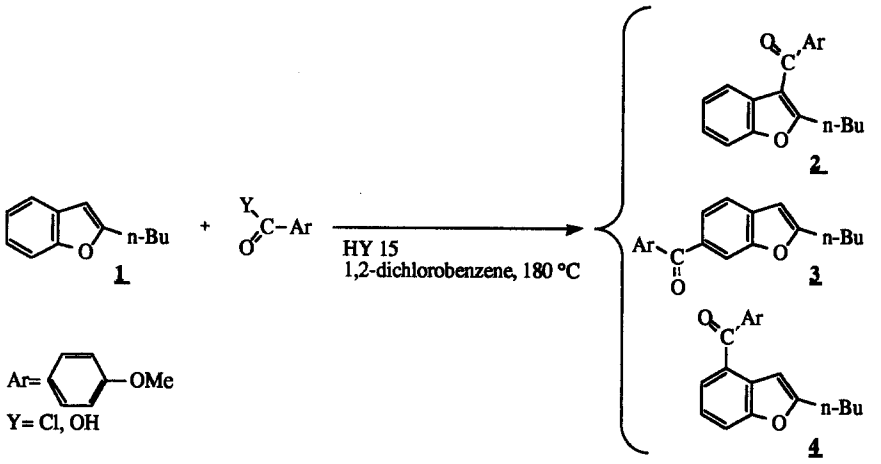


Fig. 2. Acylation of 2-butylbenzofuran with *p*-anisic acid: disappearance of **1** (○) and formation of **2** (●) versus reaction time in hours.



Scheme 1. Acylation of 2-butylbenzofuran **1** over HY zeolites.

the benzene ring (6-position preferentially and 4-position) [12]. Nevertheless, as shown in table 1, the selectivity in the 3-acylated derivative decreases with time.

A 15% decrease of the 3-acylated derivative is observed from 1 to 24 h reaction in both cases, while a concomitant increase of the two other isomers is obtained. Such a result means that the 6- and 4-isomers arise necessarily from the 3-acylated analogue. So the reaction cannot be interpreted only by a parallel mechanism scheme.

In order to explain such a behaviour, the reactivity of the 3-acylated derivative **2** was studied under various conditions.

As shown in table 2, **2**, in solution in 1,2-dichlorobenzene, is not affected when just heated at the reflux of the solvent for 24 h. In the presence of the zeolite HY 15, under the same conditions, compound **2** is partially transformed into the 2-butylbenzofuran **1** and the two acylated isomers **3** and **4**.

Table 1
Distribution of the acylated isomers with time in the acylation of 2-butylbenzofuran **1** with *p*-anisoyl chloride and *p*-anisic acid [a]

Time (h)	Y = Cl				Y = OH			
	conv. (%)	% isomers			conv. (%)	% isomers		
		2	3	4		2	3	4
1	77	87	11.5	1.5	25	82	15	2
6	80	85	13.5	1.5	45	77	20	3
8	80	83	15	2	52	75	22	3
24	80	72	25	3	72	67	28	5

[a] Conditions: see experimental part.

Table 2
Reactivity of 2-butyl-3-(4-methoxybenzoyl)benzofuran **2** in 1,2-dichlorobenzene (180°C, 24 h) [a]

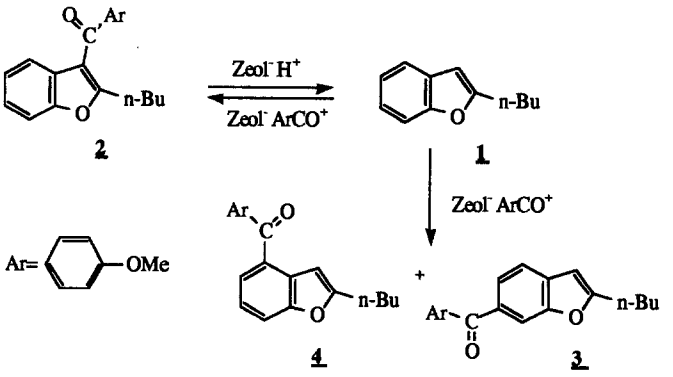
Conditions in the presence of		Unreacted **2** (%)	Products obtained (%)		
HY 15	*p*-anisic acid		**1**	**3**	**4**
no	no	100	–	–	–
yes	no	58	24	8	2
yes	yes	74	9	9	2

[a] Conditions: catalyst 0.5 g; 2.5 mmol in 50 ml 1,2-dichlorobenzene; *p*-anisic acid 2.5 mmol.

Under such conditions, the formation, in a substantial amount, of the 2-butylbenzofuran **1**, can be only explained by a deacylation reaction, occurring over the active acidic sites of the zeolite. Such a reversible Friedel–Crafts acylation has been demonstrated before, mainly for aromatics where the resonance stabilization of the acyl group with the aromatic nucleus is reduced by neighbouring bulky substituents [13,14], which, in the present case, may be due to the *n*-butyl group and the C_4–H bond. The, the formation of the two acylated isomers **3** and **4** probably occurs through a reacylation of the 2-butylbenzofuran **1** by the $ArCO^+$ acylium ion liberated during the deacylation reaction according to scheme 2.

This type of deacylation and rearrangement processes has been already proposed in the case of acylation of the 2-methoxynaphthalene over zeolites to explain the formation of the 2-acetyl-6-methoxynaphthalene from the 1-acetyl-2-methoxy isomer [15].

In order to confirm this assumption, the reactivity of the 3-acylated derivative was studied in the presence of both zeolite and acylating agent. When *p*-anisic acid is added, the amount of the deacylation product decreases (table 2). This is obviously due to the fact that, when 2-butyl benzofuran **1** is formed, it undergoes an acylation reaction with the acid present to give again the 3-acylated starting



Scheme 2. Reactivity of 2-butyl-3-anisoyl benzofuran **2** over HY zeolite at 180°C.

material **2** (15% more than without acylating agent), together with the two isomers **3** and **4**, the amounts of which do not change dramatically.

4. Conclusion

The dealuminated HY (Si/Al = 15) zeolite catalyses the acylation reaction of 2-butylbenzofuran with *p*-anisoyl chloride or *p*-anisic acid efficiently, which leads to the formation of three acylated isomers with a good initial selectivity in the 3-acylated derivative. the selectivity decreases with time, due to a consecutive deacylation of this compound, followed by a reacylation which favours the formation of the two isomers (mainly the 6-acylated one). The involvement of such deacylation–reacylation type reactions is not usual and constitutes one of the few examples ever observed over zeolites as catalysts. It is assumed that the deacylation process is due to a reduced resonance stabilization of the acyl group with the aromatic ring.

Acknowledgement

The authors gratefully acknowledge the Société SANOFI Chimie for financial support.

References

[1] E. Bisagni, N.P. Buu Hoi and R. Royer, J. Chem. Soc. (1955) 3688.
[2] N.P. Buu Hoi, E. Bisagni, R. Royer and C. Routier, J. Chem. Soc. (1957) 625.
[3] W.F. Hölderich, M. Hesse and F. Naumann, Angew. Chem. Int. Ed. Engl. 27 (1988) 226.
[4] W.F. Hölderich and H. van Bekkum, in: *Introduction to Zeolite Science and Practice*, eds. H. van Bekkum, E.M. Flanigen and J.C. Jansen (Elsevier, Amsterdam, 1991).
[5] P.B. Venuto, Microporous Mater. 2 (1994) 297.
[6] B. Chiche, A. Finiels, C. Gauthier,P. Geneste, J. Graille and D. Pioch, J. Org. Chem. 51 (1986) 2128.
[7] C. Gauthier, B. Chiche, A. Finiels and P. Geneste, Appl. Catal. 30 (1987) 365.
[8] P. Moreau, A. Finiels, P. Geneste and J. Solofo, J. Catal. 136 (1992) 487.
[9] P. Moreau, A. Finiels, P. Geneste, F. Moreau and J. Solofo, J. Org. Chem. 57 (1992) 5040.
[10] A. Finiels, A. Calmettes, P. Geneste and P. Moreau, Stud. Surf. Sci. Catal. 78 (1993) 595.
[11] F. Richard, J. Drouillard, H. Carreyre, J.L. Lemberton and G. Perot, Stud. Surf. Sci. Catal. 78 (1993) 601.
[12] A. Mustafa, *The Chemistry of Heterocyclic Compounds* (Wiley, New York, 1974).
[13] J. March, *Advanced Organic Chemistry*, 3rd Ed. (Wiley, New York, 1985).
[14] I. Agranat, Y. Bentor and Y.S. Shih, J. Am. Chem. Soc. 99 (1977) 7068.
[15] G. Harvey and G. Mäder, Collect. Czech. Chem. Commun. 57 (1992) 862.