

A new and convenient method for the acylation of amino acids in the presence of a modified zeolite: Ersorb[®]

Zoltán Hell^{a,*}, Agnieszka Cwik^a, Zoltán Finta^a, Zoltán Horváth^b

^a Department of Organic Chemical Technology, Budapest University of Technology and Economics,
P.O.B. 91, Műgyetem rakpart 3, H-1521 Budapest, Hungary

^b Erdőkémiaker Limited, Gyömrői út 132-136, H-1108 Budapest, Hungary

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Abstract

Reaction of free amino acids with acid chlorides in dioxane in the presence of a modified zeolite-type mineral Ersorb-4 results in the formation of the appropriate *N*-acyl derivatives. High yields were obtained with aryl chlorides, poorer with aliphatic ones. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

There is an increasing demand for cleaner organic syntheses in the chemical industry. This tendency enhanced the research activity for the use of catalysts and reactants which produce less waste production, but have excellent activity and selectivity even in industrial scale, and are recyclable. Large number of natural and modified zeolites fulfil these criteria and so their use in heterogeneous phase reactions has reached great development in different areas of organic syntheses [1–3]. Good results were obtained in industrial scale reactions too [4].

Ersorb-4 (E-4) is a clinoptilolite-type zeolite material with high silicium content (Si/Al ratio 5:1) [5]. The original mineral is modified with ionic exchange and with other water-phase technologies followed by a thermal treatment yielding a Ca–K mixed

cation-based adsorbent with 4 Å pore size. The composition of E-4 can be described as follows: SiO₂ 73.0%, Al₂O₃ 11.2%, Fe₂O₃ 1.17%, K₂O 5.12%, Na₂O 0.38%, CaO 2.20%, MgO 0.44%. It has a specific surface of 50 m²/g (determined by the BET method with nitrogen at the temperature of liquid nitrogen). It has high acid-proof property; its crystalline structure does not change even after a long-time treatment in hot 4 N hydrochloric acid. E-4 has a slightly surfacial acidic character [6]. The high silicium content yields high chemical resistance. It is stable until 500–600 °C. It can adsorb small molecules such as water, hydrochloric acid, ammonia, methanol or hydrogen sulfide. The small pore size does not allow the adsorption of molecules larger than the methanol in the pores. Based upon this adsorption ability, E-4 has been used as large spectral drying agent (molecular sieve) in both gaseous and liquid phases, suitable for the dehydration of gaseous hydrochloric acid or even liquid chlorine and sulfur-dioxide. When this material was treated with ammonia, the amount of Fe and Al did not change significantly, but significant Ca,

* Corresponding author. Tel.: +36-1-463-1414;
fax: +36-1-463-3648.
E-mail address: hell.oct@chem.bme.hu (Z. Hell).

Mg and K exchange was observed. The composition of this modified material (EA) can be described as follows: SiO₂ 76.7%, Al₂O₃ 12.2%, Fe₂O₃ 1.19%, K₂O 2.87%, Na₂O 0.34%, CaO 0.53%, MgO 0.13%. Its specific surface increased to 200 m²/g after 2 h heating at 500 °C. The treatment does not modify the surface acidity of the product but changes the structure of the pores and enhances the hydrogen chloride adsorbing ability [6].

The aim of our work is to check whether EA is applicable in organic syntheses, e.g. as catalyst or condensing agent. In this paper, we describe our results about the acylation of amino acids.

The *N*-acylated amino acids are useful synthons in organic syntheses but the acylation of the free amino acids might be difficult because of their low solubility in most of the organic solvents commonly used. There are only few information in the literature about this reaction; either one can use a Schotten–Baumann-type reaction in the presence of alkaline water or the acylation of an amino acid ester followed by hydrolysis. In the first method, the alkaline water may cause problems since the products are generally more soluble in water than in organic solvents and so the work-up can be difficult and the yield is often quite moderate (60–90%, no detailed data are given in [7]). In the second method, the esterification–acylation–hydrolysis sequence is time consuming and the three steps significantly reduce the overall yield. For example, in the reaction of benzoyl chloride and glycine ethylester hydrochloride in the presence of pyridine in THF for 16 h at room temperature 77% of *N*-benzoyl glycine ethylester was obtained [8]. The hydrolysis of the appropriate methylester in aqueous sodium hydroxide gave the free acid with 76% yield [9].

2. Experimental

- (1) *Pretreatment of the catalyst.* E-4 and EA are products of Erdökémia-ker, Hungary. Samples of commercially EA was powdered and heated at 120 °C for 4 h. The material thus obtained was stored in a closed bottle under dry nitrogen atmosphere.
- (2) *Acylation of amino acids with acid chlorides (general method).* To a mixture of EA (0.3 g) and the appropriate amino acid (5 mmol) in dioxane

(10 ml) acid chloride (5 mmol) was added and the mixture was heated to 100 °C for 6 h. Then the solid was filtered out, the filtrate was evaporated and the residue was triturated with diethylether or *n*-hexane. The solid thus obtained was filtered and characterized.

The spectral and physical data of the known compounds were identical with those reported in the literature (see Tables 2 and 3). The new compounds were characterized by IR and ¹H NMR spectroscopy. Spectra were made on Perkin-Elmer Model 1600 and Bruker AW-250 (250 MHz) spectrometer, respectively. *N*-(3-Chlorobenzoyl)-D-phenylglycine—IR (KBr), ν (cm⁻¹): 3420, 3305, 1712, 1641; ¹H NMR (methanol-d₄) δ (ppm): 5.66 (s, 1H), 7.36–7.53 (m, 9H), 7.79 (d, 1H). Terephthalic acid bis[(*R*)-(1-carboxy-1-phenyl)methyl]amide—m.p. 185–187 °C (ethylacetate); IR (KBr), ν (cm⁻¹): 3418, 3312, 1729, 1640; ¹H NMR (methanol-d₄) δ (ppm): 5.67 (s, 2H), 7.31–7.52 (m, 10H), 7.95 (s, 4H), 8.1 (d, 2H).

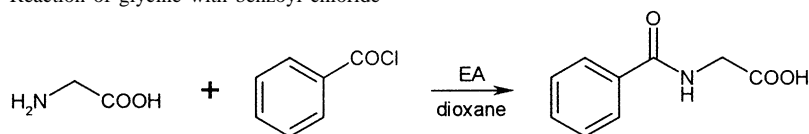
3. Results and discussion

We examined the acylation of free amino acids with different aromatic and aliphatic acid chlorides in the presence of EA. Although the free amino acids are generally well soluble in water, in the presence of EA the use of water should be avoided. They are slightly soluble in most of the organic solvents. There are some examples in the literature using a mixture of water and an ether-type solvent, e.g. dioxane for the acetylation of glycine [10]. Taking into account these facts, dioxane was chosen as solvent.

The optimal reaction conditions were determined in the reaction of glycine with benzoyl chloride. The results are shown in Table 1. The best results were obtained using 0.3 g EA/5 mmol amino acid, the increase in the amount of the catalyst did not increase in the yield significantly. This shows that the 0.3 g EA is enough for binding the 5 mmol of HCl because no gas evolution was detected from the mixture during the reaction.

In the same way, 30 mol% excess of benzoyl chloride or a reaction time more than 6 h had no advantageous effect neither. The higher temperature increased

Table 1
Reaction of glycine with benzoyl chloride



Temperature (°C)	Reaction time (h)	Benzoyl chloride/glycine (mol/mol)	EA/glycine (g/g)	Yield ^a (%)
40	5	1.0	0.3	30
100	6	1.0	0.3	75
100	6	1.0	0.4	68
100	8	1.0	0.8	70
100	6	1.3	0.8	70
140 ^b	6	1.0	0.3	0
100	6	1.0	0.3 ^c	45

^a Isolated yield.

^b Solvent: dibutyl ether.

^c Solid potassium carbonate instead of EA.

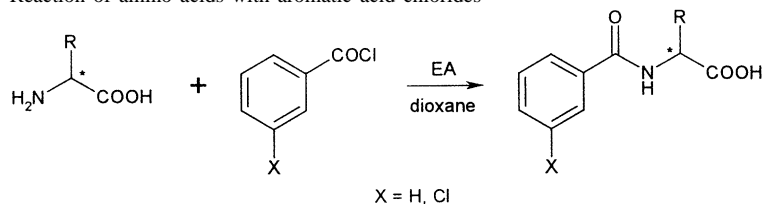
in the yield significantly. There were no other products detected in the reaction mixture.

We considered the different possibilities for binding the deliberating HCl in this acylation reaction. Reagents in homogeneous phase were excluded because both a tertiary amine, e.g. triethylamine and the excess of the amino acid would give a byproduct (triethylamine hydrochloride or glycine hydrochloride, respectively) whose solubility and other physical properties are nearly identical with the properties of the product. This way their separation would be very tedious and this could significantly decrease the yield of the product.

Compared the behavior of a heterogeneous acid binder we found that in the presence of solid potassium carbonate 45% of *N*-benzoyl glycine was obtained (see Table 1, entry 7). Further disadvantage that the potassium carbonate is not recyclable in this reaction while repeated use of EA in the reaction of glycine with benzoyl chloride proved to be successful. Thus, EA filtered from the reaction mixture was washed with water, dried, washed with chloroform and then dried at 120 °C for 4 h. Using this sample again in the acylation reaction, 72% of benzoyl glycine was obtained.

Based upon these results, we examined the reaction of different amino acids with aromatic acid chlorides.

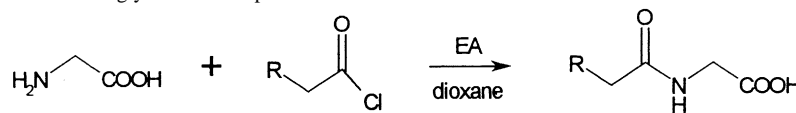
Table 2
Reaction of amino acids with aromatic acid chlorides



Amino acid	Acid chloride	Yield ^a (%)	Melting point (lit) (°C)	[α] _D (lit) (<i>c</i> = 1, methanol)
Glycine	X = H	75	186 (190–191 [11])	–
Glycine	X = Cl	73	129.5 (129–130 [12])	–
D-phenylglycine	X = H	86	188 (187–188 [13])	–105.7 (–110, <i>c</i> = 0.7, ethanol [14])
L-phenylalanine	X = H	60	178 (185–186 [15])	–35.7 (–40.3 [16])
D-phenylglycine	X = Cl	93	177	–81.1

^a Isolated yield.

Table 3

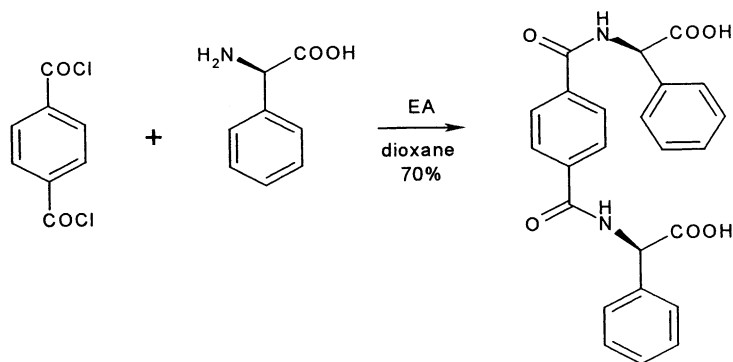
Reaction of glycine with aliphatic acid chlorides^a


Acid chloride	Reaction temperature (°C)	Yield ^b (%)	Melting point (lit.) (°C)
Acetyl	45	20	204 (206–208 [17])
Chloroacetyl	100	46	95.5 (98–100 [18])
Propionyl	70	25	125 (128 [19])

^a Reaction time: 4 h.^b Isolated yield.

The appropriate *N*-acyl compounds were obtained with good yield. The results are shown in Table 2.

Similar treatment of *D*-phenylglycine with terephthaloyl chloride in a 2:1 molar ratio resulted in the formation of the appropriate bis-amide in 70% yield. The product might be a potential resolving agent.



Reaction of glycine with aliphatic acid chlorides gave lower yields (Table 3). It seems that EA requires higher temperature for the good activity (see the results in Table 1; entries 1 and 2). Although the boiling point of the chloroacetyl chloride allowed to reach 100 °C as reaction temperature, there was no high yield obtained. At room temperature or below, no reaction was observed.

The reaction time had no effect neither: when the reaction of glycine with acetyl chloride was stopped after 1 h, the same yield (20%) was obtained as after 4 h reaction time. Not surprisingly the best result was obtained with chloroacetyl chloride, the most active compounds of the tested acid chlorides but this result

is significantly poorer than the results obtained with aromatic acid chlorides.

It is worth to mention that there are only few data in the literature about the acylation of amino acids with aliphatic compounds. Thus, e.g. for chloroacetyl glycine the only paper available described 65% yield

using chloroacetyl chloride and aqueous sodium hydroxide [20] but with a tedious work-up (several extraction with different solvents).

4. Conclusion

The modified zeolite-type adsorbent Ersorb-4 is a suitable agent for the acylation of free amino acids. The developed method is simple and convenient, the reagent can be recycled without any loss of activity. The use of the aggressive and environmentally dangerous aqueous sodium hydroxide can be avoided and the work-up of the reaction mixture is very simple.

Acknowledgements

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