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Amide Synthesis through Selective Partial Hydrolysis of Nitriles in Alkaline Media

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Abstract: Amides were obtained through partial hydrolysis of nitriles, using two different energy sources, traditional heating with solvent reflux and ultrasound. The reaction was performed at micro and semi-micro scales and at different reaction time with both energy sources. Yield was determined through gas chromatography, in the case of micro-scale and weight loss in the case of semi-micro scale.

Key words: Amide, hydrolysis of nitriles.

1. Introduction

Nitrile is one of the most important and versatile functional groupS in organic chemistry, and it can be easily transformed into several products, such as aldehydes, ketones, imines, amides, acids and heterocyclic nitrogen containing compounds like tetrazoles and oxazoles. Among these, nitriles conversion to the corresponding amides through hydrolysis is an important synthetic route that has been widely studied in organic chemistry, considering its wide industrial and pharmacological applications. Most of the amides synthetic methods are based on the reaction between carboxylic acids and amine derivatives, but these methods present several inconveniences such as the use of toxic, corrosive and expensive materials, highly exothermic reactions, low tolerance to other functional groups present in the reagents and additional purification procedures.

According to the ACS GCI Pharmaceutical Roundtable (developed by the ACS Green Chemistry Institute® and global pharmaceutical corporations), the synthesis of amides was identified as one of the most problematic reactions in the pharmaceutical industry.

Amides synthesis using transition metals catalyzed reactions are the most prevalent and selective. Transition metal complexes with metal centers such as: ruthenium [1-6], rhodium [7], palladium [8-10], gold [11-12] and nickel [13] have been widely used for this purpose. But homogeneously catalyzed reactions using metallic complexes require special handling procedures that make difficult both, the separation of the product from the catalyst and the catalyst recovery for reuse.

Another approach, trying to develop an efficient and mild process that allows the synthesis of amides from nitriles, even in the presence of other labile functional groups involves the use of ionic liquids as solvents and catalysts. Ionic liquids are considered ecological reagents in the context of green synthesis, since they provide a high solvation capacity, they possess low volatility, no flammability and can dissolve a wide variety of compounds. In this context, amides have been obtained using tetrabutylammonium hydroxide [14] (50% in aqueous media) with good results but still presenting the disadvantage of a difficult separation process between the hydrated ionic liquid and the reaction mixture.

We have developed an environmentally friendly method for the synthesis of amides through a partial selective nitrile hydrolysis reaction, using economic and ecological catalysts and reagents, using an aqueous

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media, a low concentration of sodium hydroxide and ethanol, allowing other functional groups to remain unaltered.

2. Results and Discussion

The reaction parameters were optimized using benzonitrile as model substrate in the presence of sodium hydroxide. Four reaction parameters were studied: the solvent, volume, reaction time and the sodium hydroxide concentration, as shown in Table 1.

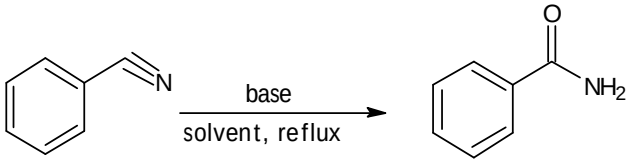
Results (Table 1) show that when 12 mL of ethanol is used in combination with a 4 *m*/*v*% sodium hydroxide concentration (Table 1, reaction 6), a yield of 84% is obtained, in contrast with the reaction where only 0.5 mL of ethanol is used (Table 1, reaction 1), where only a 50% yield is obtained. This result is explained through the low solubility of benzonitrile in the reaction mixture.

It can also be observed that as the reaction time increases the yield decreases (Table 1, reactions 6-8). The nitrile group is mechanistically intriguing as it is kinetically inert and thermodynamically unstable. Further, the rate of amide hydrolysis to the corresponding acid is much faster than the rate of hydrolysis of nitrile to the corresponding amide (Scheme 1) [15]. Based on the above, the longer reaction time we favor the kinetics of formation of the corresponding carboxylic acid

As we have mentioned previously, since benzonitrile solubility is key in obtaining the corresponding amide, we decided to evaluate different alcohols as solvents in the reaction (Table 1, reactions 9-13). When *n*-propanol was used, 5% more yield was obtained compared to ethanol, but the reaction product is easily separated from the reaction mixture when ethanol is used, obtaining better results (Table 1, reactions 6 and 10). The yields obtained using other alcohols are lower compared to the one obtained with ethanol. Ethanol behaves as an ideal solvent, according to green chemistry standards, since it is natural, nontoxic, cheap and easily available. As an additional benefit, ethanol allows for an easier separation of the product.

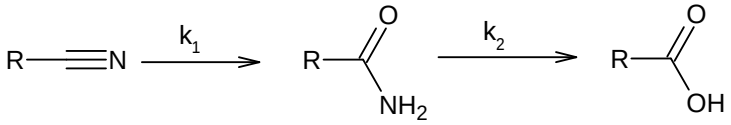
Once the reaction conditions were optimized, a variety of substituted nitriles were transformed into the corresponding amides using reflux (Table 2).

Table 1 Reaction parameters optimization.



No. of reaction	Solvent	Volume solvent (mL)	Concn. NaOH *m*/*v* %	Volume NaOH (mL)	Reaction time (h)	Reaction yield (%)
1	Ethanol	0.5	4	4	2	50
2	Ethanol	0.5	7.7	15	2	8
3	Ethanol	12	1.1	15	2	57
4	Ethanol	12	7.7	15	2	74
5	Ethanol	12	29	4	2	52
6	Ethanol	12	4	4	2	84 66[b]
7	Ethanol	12	4	4	2.5	38
8	Ethanol	12	4	4	3	30
9	Methanol	12	4	4	2	27
10	*n*-propanol	12	4	4	2	89 39[b]
11	*n*-butanol	12	4	4	2	56
12	Iso-butanol	12	4	4	2	35
13	1,4-butanediol	12	4	4	2	79

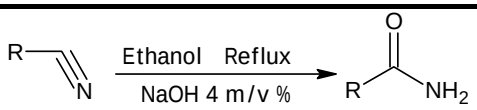
Reaction conditions: 1 mmol of benzonitrile; Yield was calculated by gas chromatography. [b] Product yield isolated.

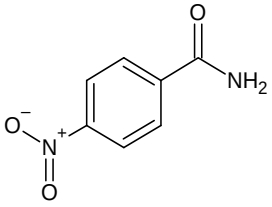
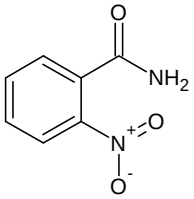
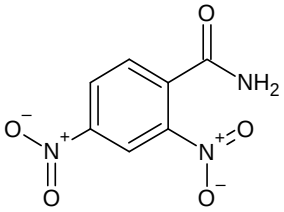
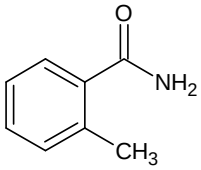
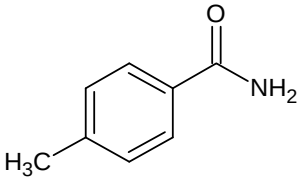
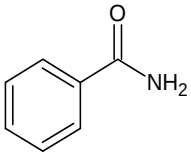
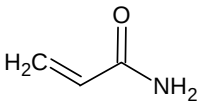


Scheme 1. Hydration of the nitriles to the amides.

Nitrile group is kinetically inert and thermodynamically unstable [15]. $k_1 < k_2$.

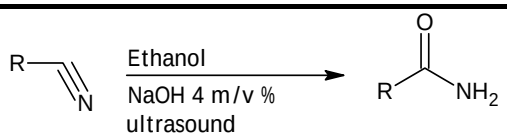
Table 2 Substituted nitriles.

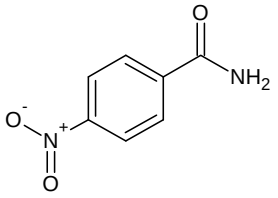
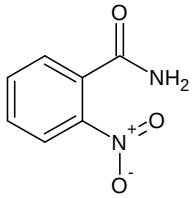
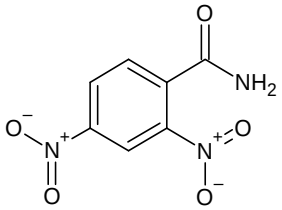
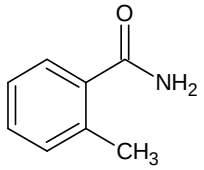
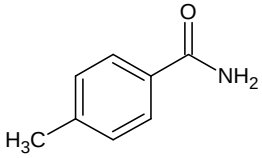
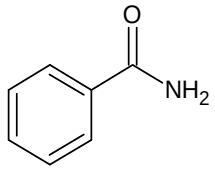
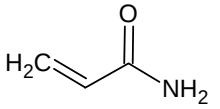


No. of reaction	Product	Time (h)	Yield (%)
1		1	54
		1.5	66
		2	84
2		1	25
		1.5	20
		2	16
3		1	19
		1.5	26
		2	12
4		1	c
		1.5	c
		2	c
5		1	63
		1.5	78
		2	97
6		1	68
		1.5	73
		2	85
7		1	48
		1.5	52
		2	76

Reaction conditions: nitrile, 1 mmol, 12 mL ethanol, 4 mL sodium hydroxide 4 *m*/*v* %; Yield was obtained through gas chromatography; c: No reaction was observed.

Table 3 Reactions using ultrasound as energy source.



No. of reaction	Product	Time (h)	Yield (%)
1		1	55
		1.5	79
		2	71
2		1	6
		2	20
		3	26
3		1	c
		1.5	c
		2	c
4		1	c
		1.5	c
		2	c
5		1	c
		1.5	c
		2	c
6		1	43
		1.5	57
		2	55
7		1	36
		2	34
		3	29

Reaction conditions: nitrile, 1 mmol, 12 mL ethanol, 4 mL sodium hydroxide 4 *m*/*v* %; Yield was obtained through gas chromatography; c: No reaction was observed.

As Table 2 shows, aromatic nitriles with electron donating groups such as *p*-methyl, *o*-methyl or substituents with electron withdrawing groups such as 2-nitro and 2,4-dinitro, exhibit a comparable reactivity and react in most cases to produce the desired amide. The only case where the reaction did not proceed at all is the one involving a methyl group in ortho position respect to the nitrile group (Table 2, reaction 4). One explanation to this lack of reactivity would be that the methyl group acts as an electron donor, which reduces

the electrophilic character of the nitrile carbon atom, making it less reactive towards nucleophilic attacks, which, combined with the steric hindrance produces a zero yield reaction. Steric hindrance is also observed in reaction number 2 (Table 2) where the nitro group in ortho position diminishes significantly the yield respect to reaction 1 (Table 2).

In addition to a classical reaction energy supply through heat, we also explored an alternative energy source, such as ultrasound energy. Ultrasound has been applied to chemical reactions offering the chemist an alternative way of activating chemical groups using a relatively economical equipment. The driving force in sonochemistry is cavitation, and it requires that at least one of the phases in the reaction mixture is a liquid.

The use of sonochemistry in synthesis has become increasingly relevant in recent years and the interest has gone beyond academic laboratories, reaching now engineering chemistry processes and the chemical industry [16-17].

Comparing the results obtained in Tables 2 and 3, we can analyze the effect of changing the energy source in the reaction. When ultrasound is used in the reaction of *p*-methyl benzonitrile (Table 2, reaction 5), after 2 h, the yield is already 97%, in contrast with the same reaction but using ultrasound (Table 3, reaction 4), where the reaction did not proceed at all. This trend is repeated in all cases, since the yield is always lower in the reactions that used ultrasound in contrast with the ones that used traditional heating with reflux.

3. Experimental Procedure

3.1 Experimental Procedure to Calculate Yield Using Gas Chromatography

In a 25-mL round bottom flask, equipped with a magnetic stirrer, 1 mmol of the corresponding nitrile was added, together with 4 mL sodium hydroxide 4 *m*/*v* % and 12 mL ethanol. A condenser is set on top of the flask and the reaction is heated during the desired reaction time.

The flask is then cooled at room temperature and then it is cooled using a water/ice mixture. The mixture is neutralized using HCl_{aq} (37 *m*/*m* %) up to a pH equal to 7 using pH paper or using a potentiometer and the reaction mixture is poured into a 25-mL volumetric flask. HPLC (high-performance liquid chromatography) grade methanol is added until the solution reaches the mark. Subsequently, 1 μL of solution is injected into the gas chromatograph.

3.2 Product Isolation Procedure

In a 125-mL round bottom flask, equipped with a magnetic stirrer, 5 mmol of the corresponding nitrile was added, together with 20 mL sodium hydroxide 4 *m*/*v* % and 60 mL ethanol. A condenser is set on top of the flask and the reaction is heated during the desired reaction time.

The flask is then cooled at room temperature and then it is cooled using a water/ice mixture. The mixture is neutralized using HCl_{aq} (37 *m*/*m* %) up to a pH equal to 7 using pH paper or using a potentiometer. Solvent was evaporated using a rotary evaporator and the remaining liquid is poured into a beaker, which is cooled at room temperature and then using a water/ice mixture, until a precipitate is obtained.

The precipitate is washed with a 1:1 water/ethanol cool mixture and let dry. The solid melting point is measured to confirm that the desired product is obtained, a thin layer chromatography is also performed to verify the absence of sub-products and the yield is calculated weighting the obtained solid.

FTIR (Fourier-transform infrared spectroscopy) and ^{1}H-NMR (^{1}H-nuclear magnetic resonance) are performed to confirm that the product obtained is the corresponding amide.

3.3 Ultrasound

In a 25-mL erlenmeyer flask, 1 mmol of nitrile, 4 mL of NaOH 4 *m*/*V*% and 12 mL of EtOH are added.

The tip of the ultrasound is introduced to the reaction mixture, the equipment is configured with the

desired time at 130 W, 20 kHz and Ampl. 30%. Once the time has ended the reaction mixture is placed in a water/ice bath, neutralized with HCl_{aq} (37 *m*/*m* %), the pH is verified to be equal to 7 with the help of a pH paper. The mixture is transferred to a round bottom flask and with the help of a rotary evaporator the excess EtOH is evaporated. Pour the mixture into a 25-mL beaker, allow the mixture to cool to room temperature, then place the beaker in a water/ice bath until the solid precipitates. Filter and wash with a cold 1:1 (water:ethanol) mixture.

3.4 IR Spectroscopy

Approximately 20 mg of sample is taken, added in an agate mortar and homogenized.

Subsequently, anhydrous KBr is added and the mixture is homogenized, finally a small amount is taken and put into the compactor.

The IR analysis is performed.

(1) Benzamide

White solid, IR (KBr, cm^{-1}): 3,764, 3,367, 3,172, 3,055, 1,660, 1,621, 1,575, 1,454, 1,401, 1,296, 1,143, 1,120, 1,024, 920, 787, 686, 634, 528, 415. ^{1}H-NMR (60 MHz, DMSO, ppm): δ = 7.969 (bs, 1H), 7.87 (d, 2H), 7.513 (t, 1H), 7.48 (t, 2H), 7.4 (bs, 1H) (Figs. 1 and 2).

(2) 2-nitrobenzamide

Brown solid; IR (KBr, cm^{-1}): 3,363, 3,178, 1,658, 1,623, 1,573, 1,524, 1,486, 1,408, 1,358, 1,307, 1,125, 856, 785, 698, 671, 552 (Fig. 3).

(3) 4-nitrobenzamide

Brown solid; IR (KBr, cm^{-1}): 3,417, 3,315, 3,113, 1,663, 1,592, 1,513, 1,406, 1,341, 1,119, 866, 762, 697, 644, 608. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO, ppm): δ = 8.371-8.016, 7.556, 6.873 (Figs. 4 and 5).

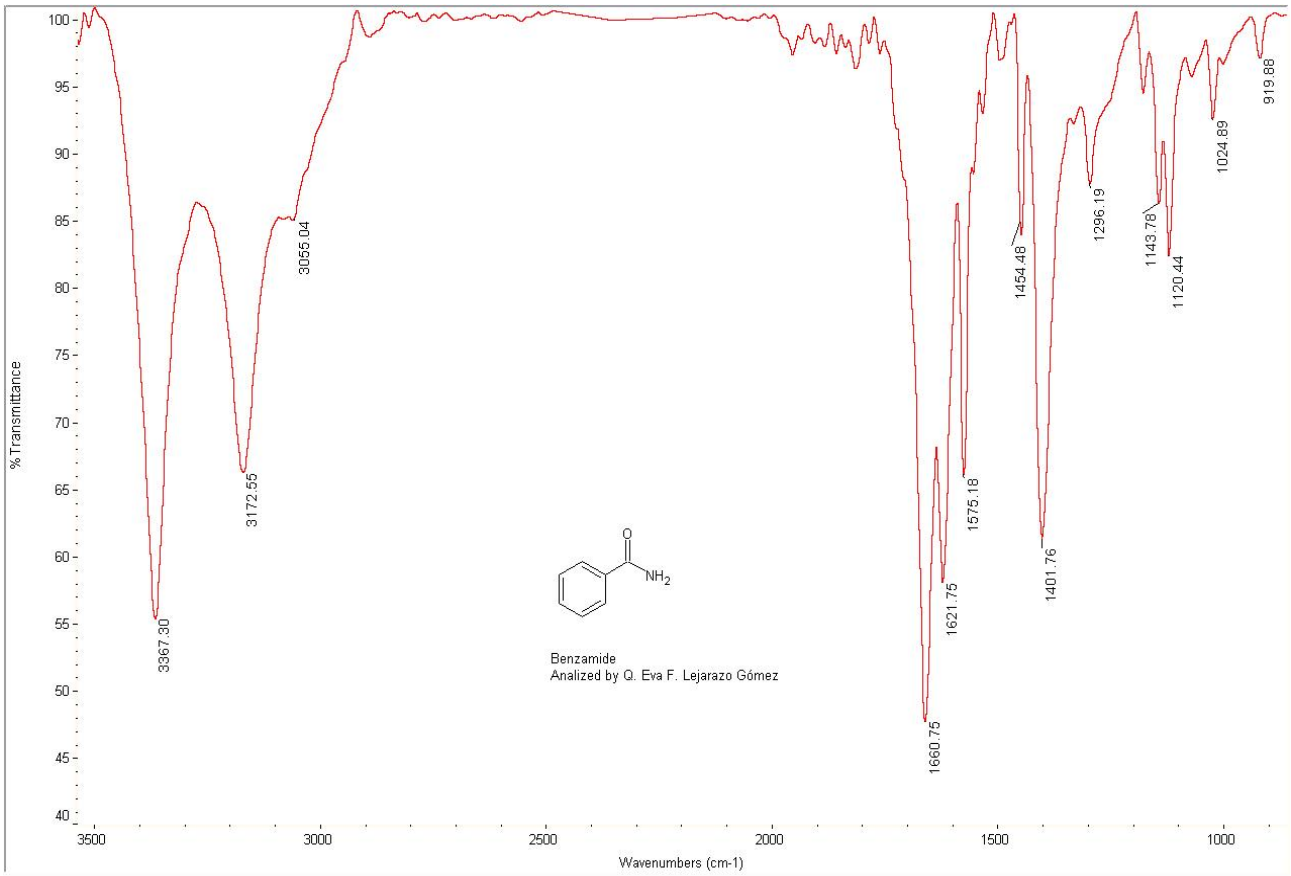


Fig. 1 IR of Benzamide.

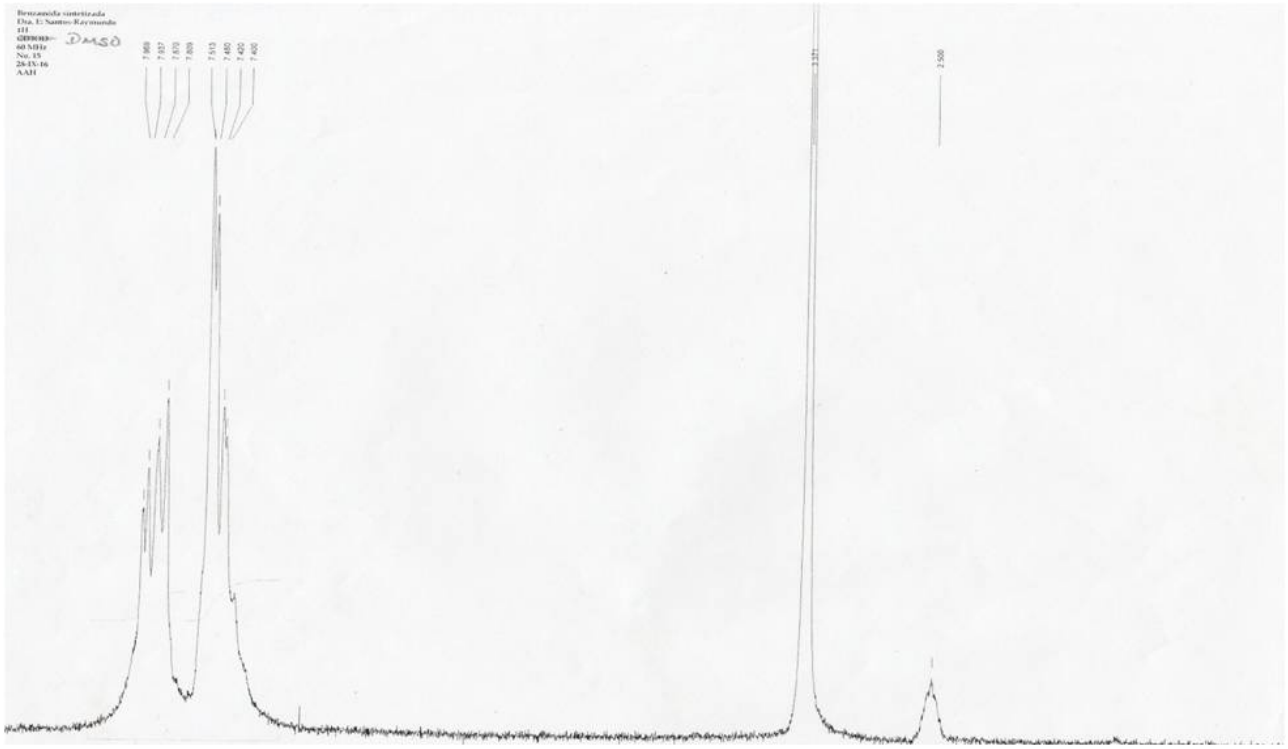


Fig. 2 ^{1}**H-NMR of Benzamide.**

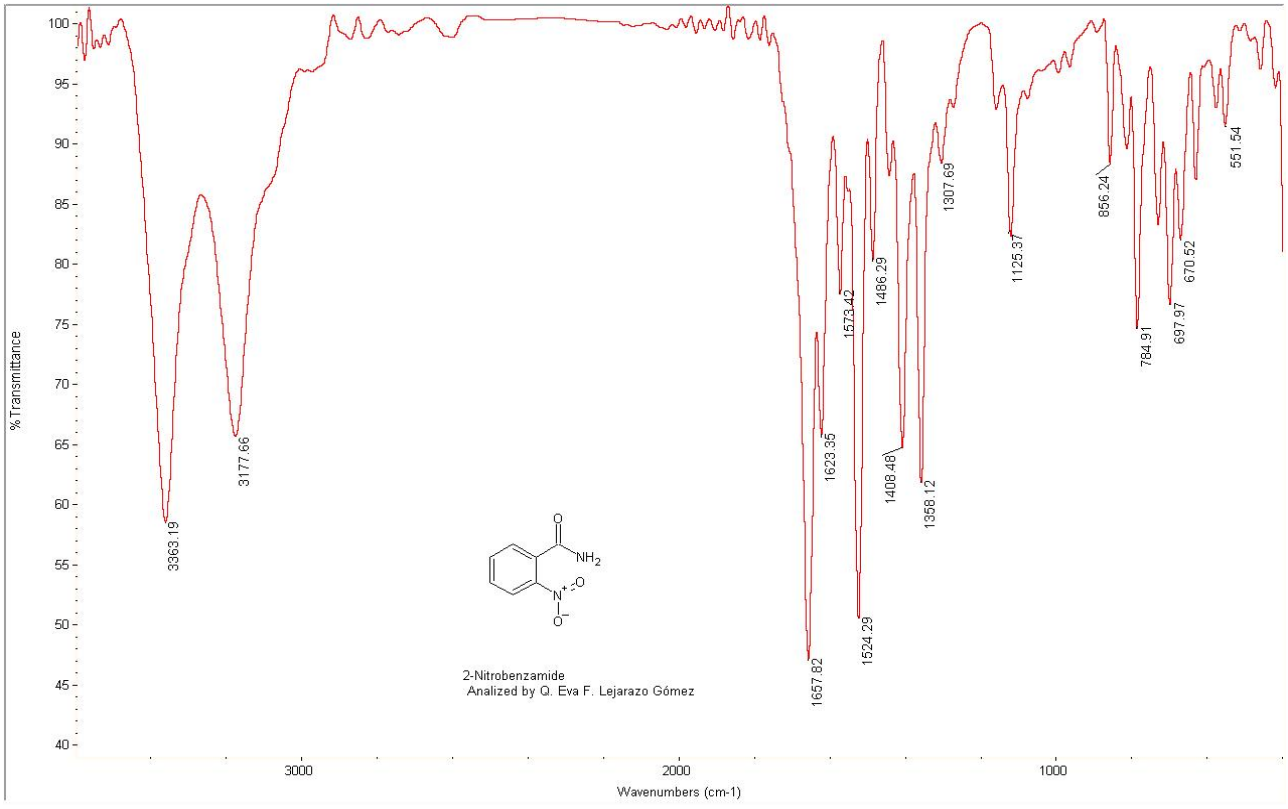


Fig. 3 **IR of 2-nitrobenzamide.**

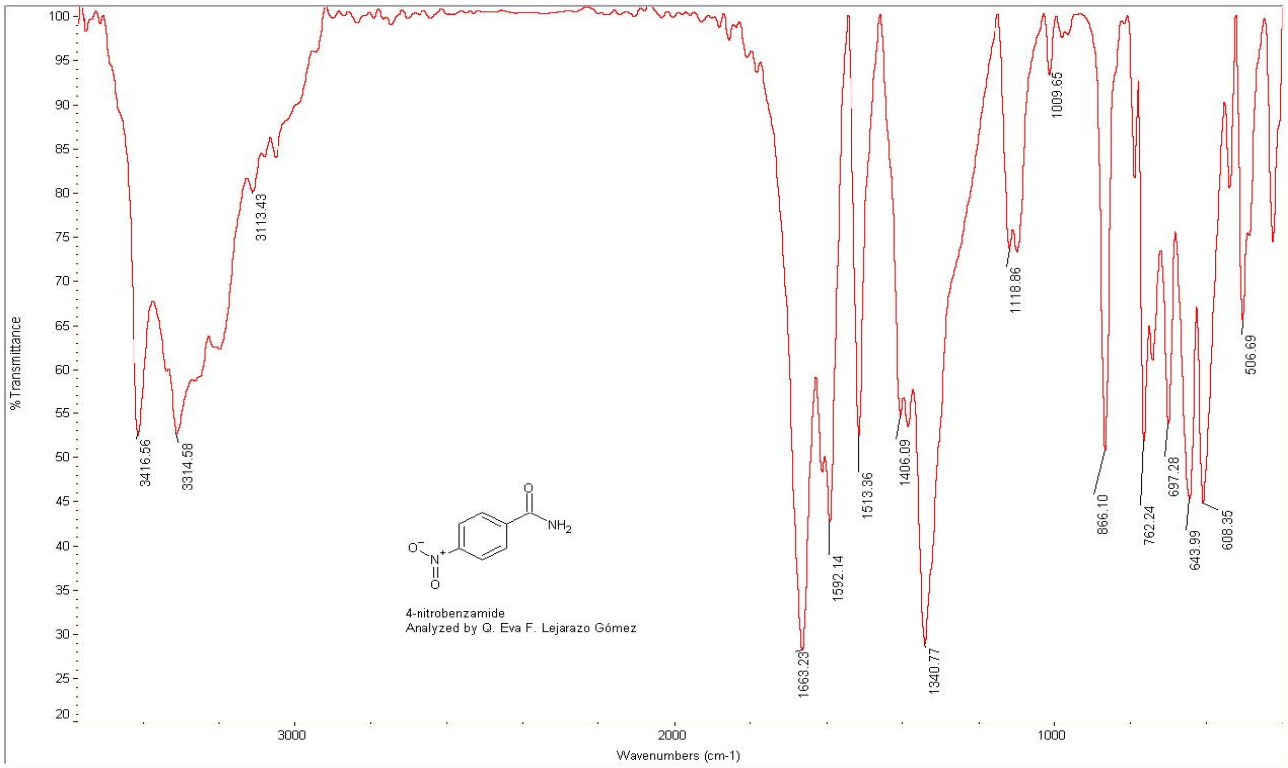


Fig. 4 IR of 4-nitrobenzamide.

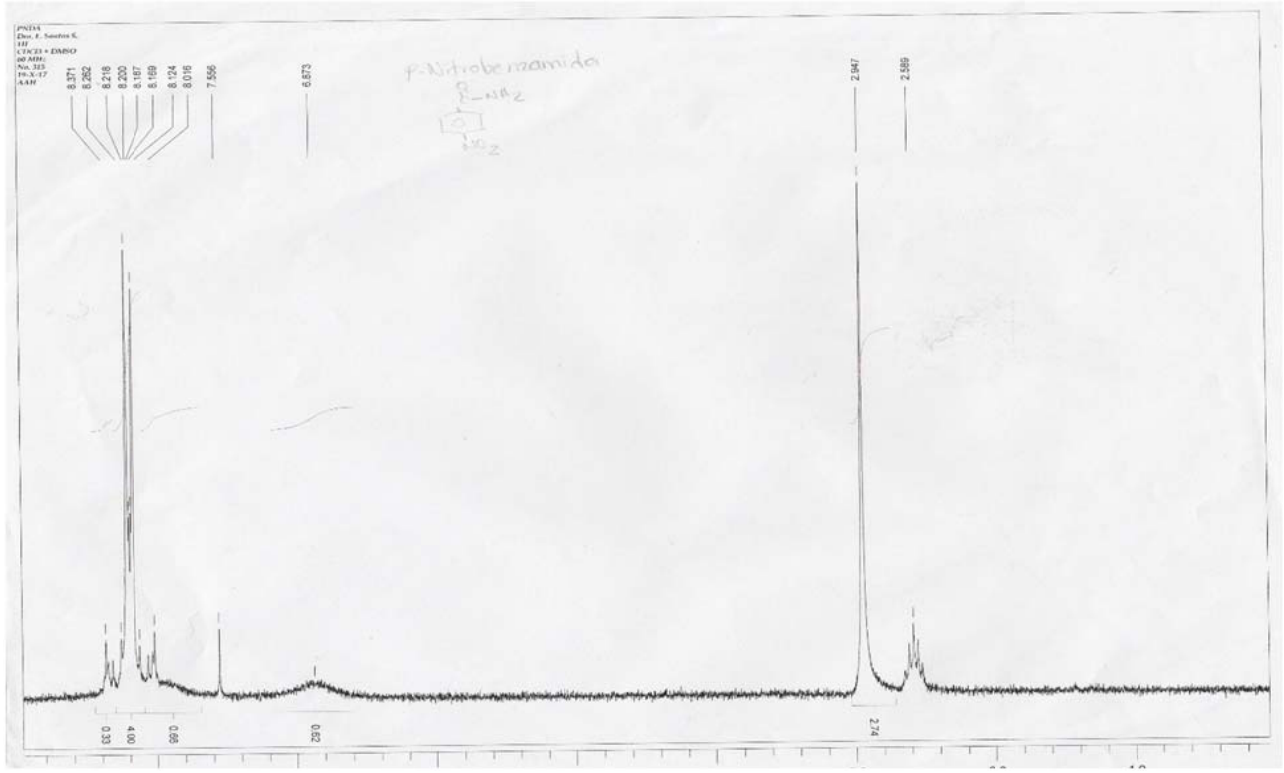


Fig. 5 ^{1}H-NMR of 4-nitrobenzamide.

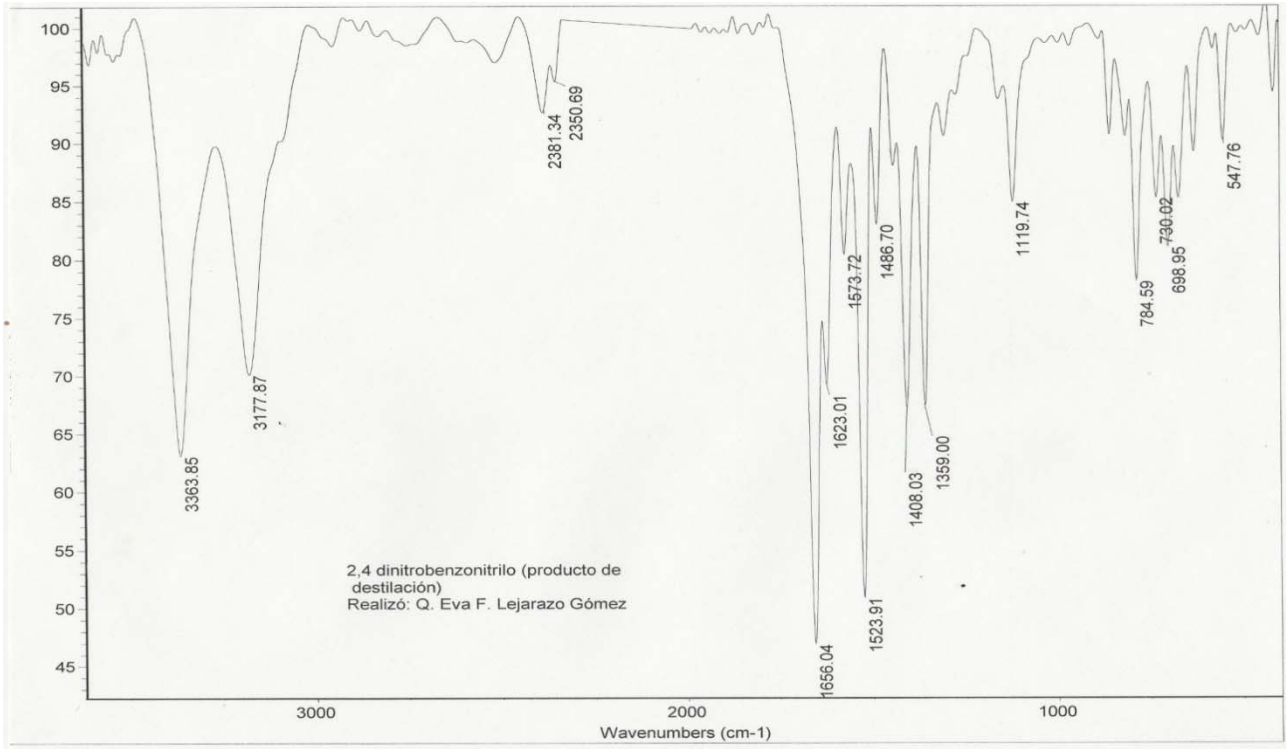


Fig. 6 IR of 2,4-dinitrobenzamide.

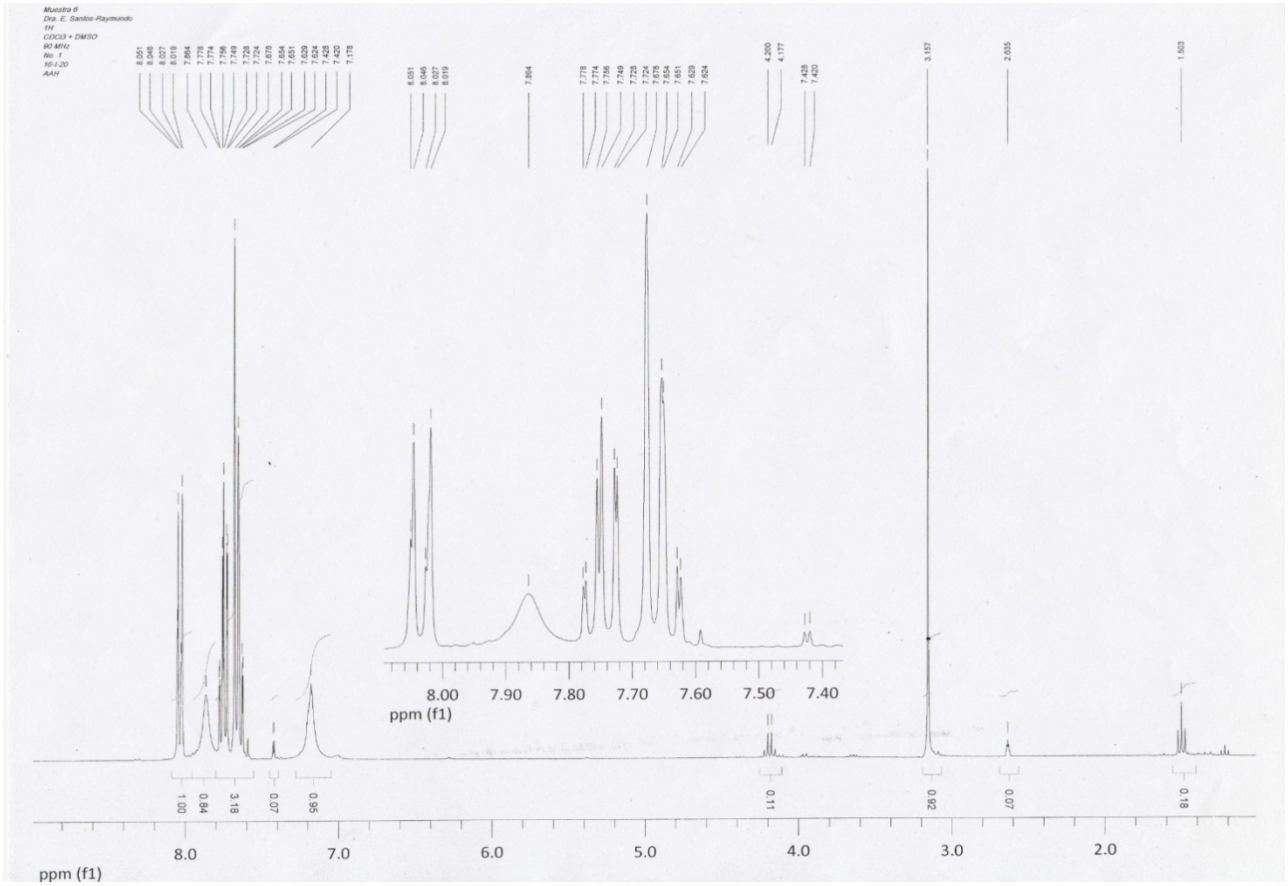


Fig. 7 ^{1}H-NMR of 2, 4-dinitrobenzamide.

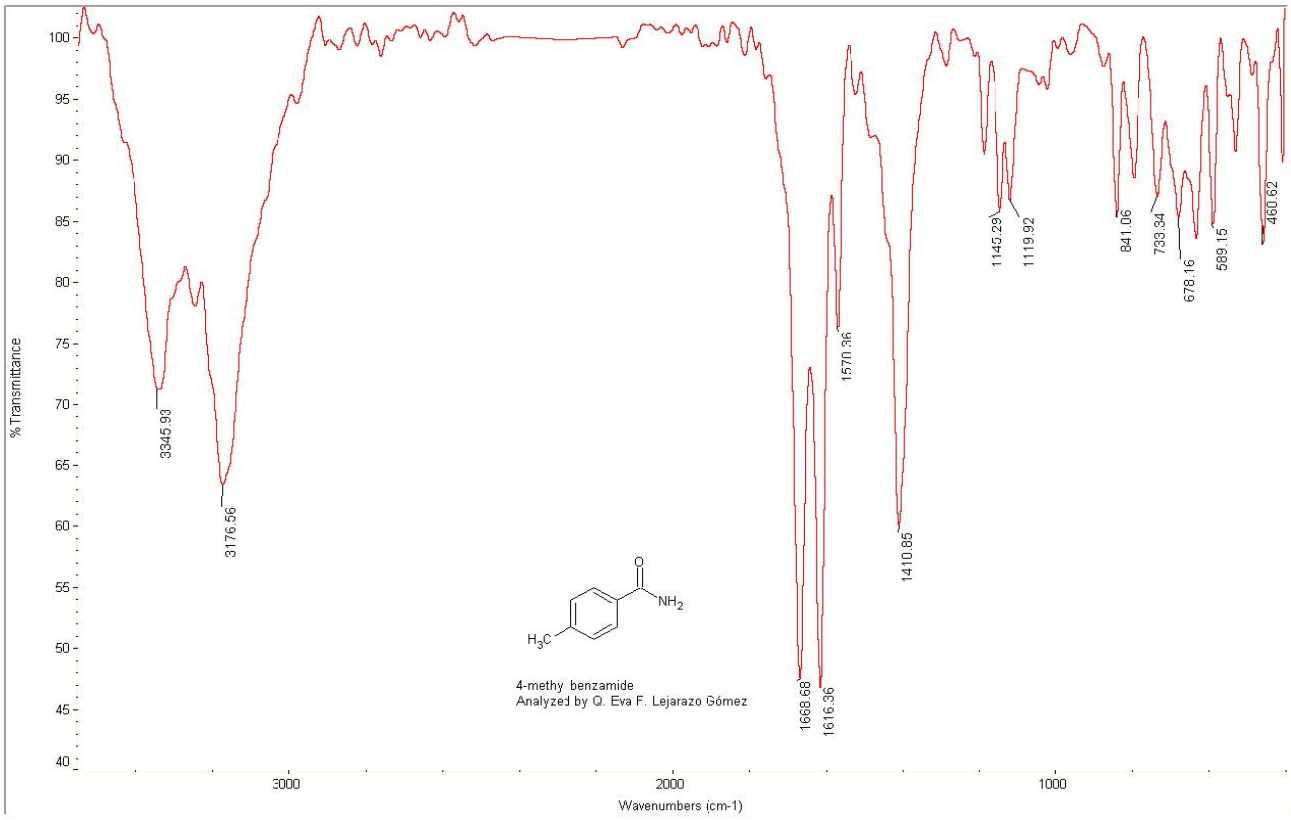


Fig. 8 IR of 4-methylbenzamide.

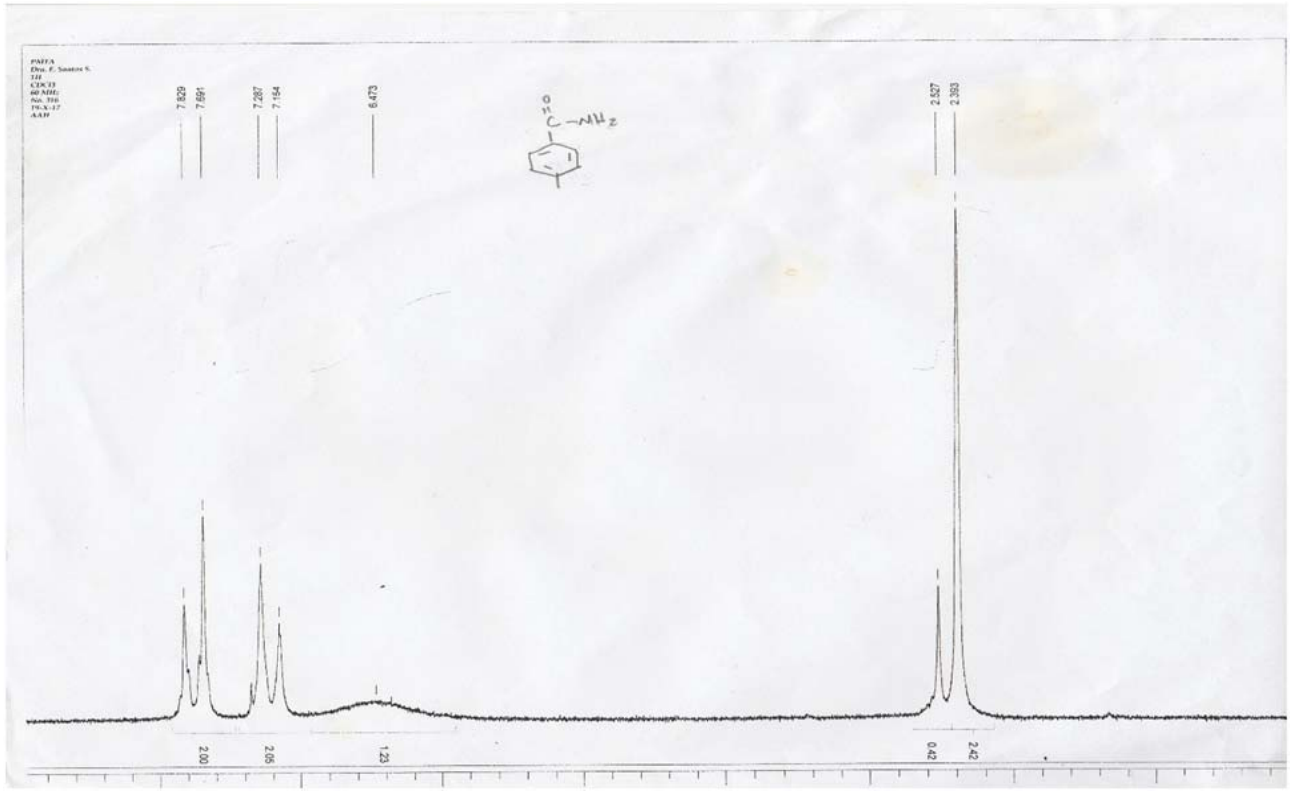


Fig. 9 ^{1}H-NMR of 4-methylbenzamide.

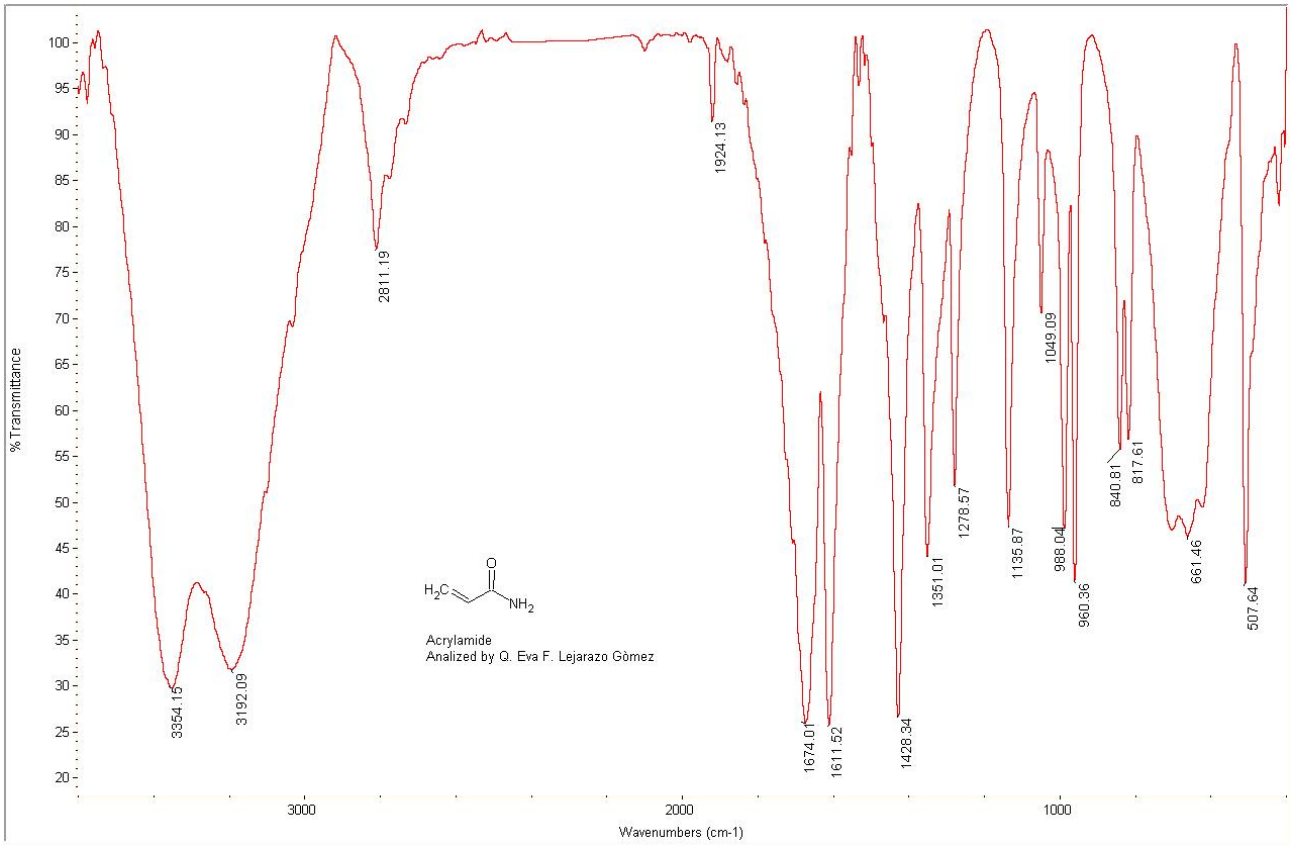


Fig. 10 IR of acrylamide.

(4) 2,4-dinitrobenzamide

Brown solid; IR (KBr, cm^{-1}): 3,112, 2,992, 1,590, 1,531, 1,425, 1,400, 1,352, 1,302, 1,267, 1,089, 1,034, 966, 875, 811, 737, 615, 511. ^{1}H-NMR (90 MHz, $CDCl_3$ + DMSO, ppm): 8.051-8.019, 7.778, 7.774, 7.756, 7.749, 7.728, 7.724, 7.678, 7.651 (Figs. 6 and 7).

(5) 4-methylbenzamide

White solid; IR (KBr, cm^{-1}): 3,348, 3,178, 1,669, 1,616, 1,567, 1,411, 1,184, 1,148, 849, 591. ^{1}H-NMR (60 MHz, $CDCl_3$, ppm): 7.83, 7.69, 7.29, 7.15, 2.53, 2.39 (Figs. 8 and 9).

(6) Acrylamide

White solid; IR (KBr, cm^{-1}): 3,354, 3,192, 2,811, 1,974, 1,674, 1,612, 1,428, 1,351, 1,279, 1,136, 1,049, 988, 960, 841, 818, 661, 508 (Fig. 10).

4. Equipment

- Gas chromatograph: HP 5890 Hewlett Packard. Equipped with a capillary column: DB5, 30 m × 0.57 μm internal diameter and a Flame ionization detector. The injector is heated at 295 °C and the detector at 250 °C; column temperature program: T_i = 170 °C × 2 min, then a ramp of 2 °C/min up to T_2 = 250 °C for 11 min. And then the same ramp of 2 °C/min up to T_f = 295 °C for 2 min;
- Ultrasound: model CPX 130;
- Nicolet Impact 410 Spectrometer.

5. Reagents

(1) Sodium hydroxide RA was acquired from Sigma Aldrich;

(2) Ethanol (96%) undenatured was acquired from Conquimex;

(3) Benzonitrile, anhydrous (≥ 99%) acquired from Sigma Aldrich;

(4) *p*-tolunitrile 98%, acquired from Sigma Aldrich;

(5) 2-nitrobenzonitrile synthesized in the laboratory [18, 19];

(6) 4-nitrobenzonitrile 97%, acquired from Sigma Aldrich;

(7) 2,4-dinitrobenzonitrile 97%, acquired from Sigma Aldrich;

(8) *o*-tolunitrile 97%, acquired from Sigma Aldrich;

(9) HCl (37 *m*/*m* %) acquired from Reactivos CIVEQ;

(10) Methanol 99.93% A.C.S HPLC grade, acquired from Sigma Aldrich;

(11) 1-propanol, acquired from J.T Baker;

(12) 1-butanol acquired from J.T Baker;

(13) iso-butanol, acquired from J.T Baker;

(14) 1,4-butanediol, acquired from Aldrich Chemical Company Inc.

6. Conclusions

Ultrasound, as an alternative energy supply shows advantages in terms of a better reaction system handling, but, it does not necessarily represent a benefit in terms of reaction yield.

In this case the partial hydrolysis of nitriles using heating through reflux provides better yields, up to 80% in the presence of sodium hydroxide, ethanol and water.

The procedure described in this document is an efficient, nonpolluting alternative for the synthesis of amides, in contrast with other procedures described in the literature, which considers the use of organometallic catalysts.

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