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# Towards Green Synthesis of Fatty Alkanilides

**F. Malki*[1], A. Touati[1], S. Moulay[2], M. Baltas[3]**

[1]*Laboratoire de Recherche sur les Produits Bioactifs et Valorisation de la Biomasse, Ecole Normale Supérieure, BP 92, Vieux Kouba, Algiers, Algeria.*

[2]*Laboratoire de Chimie-Physique Moléculaire et Macromoléculaire, Département de Chimie Industrielle, Faculté de Technologie, Université Saâd Dahlab de Blida 1, B. P. 270, Route de Soumâa, 09000, Blida, Algeria.*

[3] *Laboratoire de Synthèse et Physicochimie de Molécules d'Intérêt Biologique, UMR 5068, Université Paul Sabatier, 118, route de Narbonne -31062 Toulouse Cedex 9, France.*

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*malki_fatiha76@yahoo.fr*
*Phone: +213773772530*

## Abstract

On the one hand, fatty alkanilides were synthesized in good yields (>70%) in solvent-free reaction from the corresponding fatty acids and aniline. On the other hand, synthesis of *n*-dodecanilide or lauranilide, out of these alkanilides, was investigated in aqueous medium and in the presence of *p*-dodecylbenzenesulfonic acid (DBSA) as a Brønstëd acid surfactant/combined catalyst, or in the presence of a lanthanide triflate as Lewis acid catalyst.

## 1. Introduction

Water is considered an environmentally friendly solvent for a number of synthetic reactions because it is readily available, nontoxic, cheap, safe and harmless [1]. However, most of organic compounds are water insoluble. Fortunately, the use of surfactant alleviates this insolubility hampering, and, besides, the surfactant may efficiently acts as a catalyst in organic reaction occurring in aqueous medium [2]. Surfactant-catalyzed organic reactions in water have turned to be one of the most challenging research issues [3].

Brønstëd acids and Lewis acids as surfactant-type acids can catalyze organic reactions without using harmful organic solvents. They have demonstrated a dual role in organic reactions as catalyst to activate substrate molecules and as a surfactant to increase the concentration of organic reactants to form micelle particles in water [4].

*p*-Dodecylbenzenesulfonic acid (DBSA) is a Brønstëd acid surfactant-combined catalyst, which is composed of an acidic group and a hydrophobic moiety. It could be explained that the inside of emulsion droplets composed of substrate and DBSA is hydrophobic enough to exclude water molecules. The behavior of DBSA as a catalyst has been studied in various reactions [3].

Lewis acid catalysis has been of great interest in organic synthesis. Furthermore, Lewis acid surfactant-combined catalysts, another type of Lewis acid catalyzing reactions in water without using any organic solvents, have been also developed [5]. Some of the most important transformations in organic chemistry result in the formation of carbon–carbon and carbon–heteroatom bonds, and both of these bonds can be formed using lanthanide triflate [Ln(OTf)3]-containing precatalysts. Lanthanide triflates are reusable, easy-to-handle, and can function as strong Lewis acids in both aqueous and non-aqueous solvent mixtures [6].

Hasaninejad *et al.* reported the application of combined Lewis acid-surfactant catalyst [aluminum tris (dodecyl sulfate) trihydrate [Al(DS)3·3H2O] for the synthesis of 1,8-dioxo-octahydroxanthens and 1,8-

dioxodecahydroacridines under solvent-free conditions and water is used as a green solvent for the synthesis of 1, 8-dioxo-decahydroacridines. The high selectivity and high isolated yields of this transformation are important [7].

Anilides are an important class of compounds that received a widespread interest in recent years because of their diverse biological activities [8-10]. The derivatives of anilides are widely used as antimicrobial [11, 12] anticonvulsant [13], anaesthetic [14], antiproliferative [15], and antiplaque agents [16], and for antiplatelet aggregation as well [17]. They are also involved as intermediate products in the synthesis of therapeutic agents [18]. Recently, some of their derivatives were screened for their antioxidant activity [19-21]. A standard method of their synthesis is based on the dehydration between a carboxylic acid and aniline under anhydrous conditions and at elevated temperatures [22]. Direct dehydration in water can be realized by using surfactants, which can partially solubilize the involved organic compounds and /or form emulsion with them in water [1, 23-26]. Fatty alkanilides have been commonly made by reaction of the acid chloride of the corresponding fatty acids with aniline and their derivatives in diethyl ether and the yields were generally moderate [27, 28]. Besides being a two-step synthesis, the latter protocol involved the use of an organic solvent.

In continuation of our previous work [29, 30], we wish to report the results of the application of the neat reaction to the synthesis of fatty alkanilides, and of a study of the impacts of water as a reaction medium, *p*-dodecylbenzenesulfonic acid (DBSA) as a Brønstëd acid surfactant/combined catalyst, and lanthanide triflate/sodium dodecylsulfate (SDS) as a Lewis acid catalyst/surfactant system, on the synthesis of *n*-dodecanilide, a fatty alkylamide.

## 2. **Experimental**

All chemicals and solvents were purchased from Fluka, Merck and Schuchardt. Methylene chloride was dried over anhydrous calcium chloride and distilled over phosphorus pentoxide. TLC plates, made of silica and alumina gels, were supplied by Merck. Infrared spectra were recorded with FTIR Perkin Elmer 457. UV spectra were taken using PyeUnicam SP8 UV/vis and a double beam Schimadzu UV-vis type 160. $^1$H NMR spectra were realized on Varian 411 spectrometer. Melting points were measured using a Büchi 220 V capillary melting point apparatus. The type of mass spectroscopy used in our work was NERMAG R 10-10 spectrometer.

### 2.1 *General procedure for synthesis of alkanilides under neat conditions*

The alkanilides were prepared according to the Webb procedure [22, 31]. The reactions involved the use of an excess of aniline and the corresponding fatty acids; water was removed by distillation. Yields and melting points are compiled in Table1. The alkanilides were characterized by the different spectral analyses and the data were found to be in agreement with those of the assigned molecular structures. Overall, their different spectra were identical. As an example, the following are the spectral characteristics of dodecanilide ($R = CH_3\ (CH_2)_{12}$ –).

IR(KBr), $\nu$ (cm$^{-1}$): 3300 (NH), 1655 (C = O), 1310 (C-N).

UV (cyclohexane), $\lambda_{max}$ (nm), ($\varepsilon$): 241, (12375).

$^1$H NMR ($CDCl_3$), $\delta$ (ppm): 7.2-7.4 (NH, $H_{arom}$), 2-2.35 ($\alpha$ $CH_2$), 1.6-1.7 ($\beta$ $CH_2$), 1.25 ($(CH_2)_n$), 0.88 ($CH_3$).

MS*:* 275.2259.

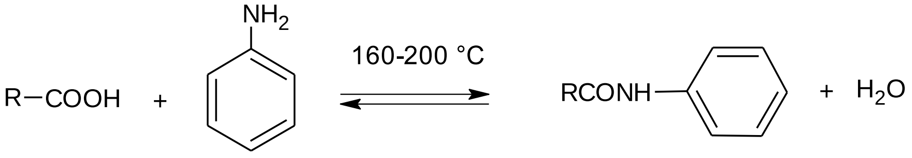
### 2.2 *General procedure for synthesis of dodecanilide in aqueous organized medium*

Into a 25-mL round-bottomed flask were charged 1.5-3 mL of an aqueous solution of surfactant, 1 mmole of dodecanoic acid, 1.7 mmoles of freshly distilled aniline. The reaction mixture was allowed to stir at 45 °C and was monitored by means of TLC technique. After 48 h, saturated aqueous solutions of $NaHCO_3$ and of NaCl (or KCl) were added. then extracted by using ethyl acetate. The product was 5% aqueous solution of HCl was added to the organic layer to remove the excess of aniline. The ethyl acetate layer was then washed with saturated aqueous solution of salt, dried over anhydrous $Na_2SO_4$, and finally ethyl acetate was evaporated. The alkanilide was recrystallized from ethanol.

## 3. Results and discussion

### 3.1. *Solvent-free reaction*

Fatty alkanilides were first prepared via a solvent-free or neat reaction by the conventional method as described earlier by Webb [22]. (Eq.1) and the results are compiled in Table 1. The different alkanilides were obtained as white crystals in yields as high as 73-96%. It can be noticed that the melting point roughly increased with alkyl chain length. The different *n*-alkanilides showed low solubility in water, and good solubility in ethanol, diethyl ether, acetone, chloroform and methylene chloride. The main drawbacks of this synthetic procedure were the elevated working temperature, from 160 to 200 °C, and the concomitant removal of the formed water.



$R = C_nH_{2n+1}$ (n = 9, 11, 13, 15, 17)

(Eq. 1)

**Table 1**: Yields and melting points of the different fatty alkyanilides

| R | Yield (%) (Lit.) | m.p. (°C) (Lit.) | MS (m/z) |
|---|---|---|---|
| $CH_3(CH_2)_8$ – | 84 | 64-65 | -- |
| $CH_3(CH_2)_{10}$ – | 73 (43.60 [27]) | 76-78 (52-54 [27]) | 275.2259 |
| $CH_3(CH_2)_{12}$ – | 96 (42.20 [27],68 [28]) | 83-84 (49-51 [27].), 71-74 [28]) | 303.2556 |
| $CH_3(CH_2)_{14}$ – | 74.50 | 88-90 | -- |
| $CH_3(CH_2)_{16}$– | 95.50 (26.40 [27]) | 89-91(57-59 [27]) | 359.3184 |

### 2.2 *Water as a reaction medium*

In the aim to work under mild conditions and to circumvent the above shortcomings, the synthetic reaction for dodecanilide ($R = CH_3\,(CH_2)_{12}$ –) was run in water at 45 °C for 48 h as a reaction model. During the reaction, a milky aspect was constantly observed and disappeared as soon as the stirring was ceased. Dodecanoic acid could have also acted as pseudo-surfactant, generating unstable micelles. The yield was miserably low, nearly 5%; this low yield could be due unequivocally to the low water solubility of both dodecanoic acid and aniline, and to the hydrolytic decomposition of the formed dodecanilide. Thin layer chromatography (TLC) analysis indicated the formation of one product. UV-visible analysis revealed a band at $\lambda_{max} = 241$ nm, assigned to $\pi \rightarrow \pi^*$ for dodecanilide. The IR spectrum showed a conspicuous band at 1655 $cm^{-1}$, attributable to the carbonyl of the amide group.

### 2.3 *Micellar medium*

The second step was to conduct the reaction in water and in the presence of a surfactant (Eq. 2). The use of surfactant is doubly-faceted, a solubilizing agent and a reaction catalyst. For this purpose, sodium dodecylsulfate (SDS), an anionic surfactant, and cetyl trimethylammonium bromide (CTAB), a cationic one, were examined.

$$C_{11}H_{23}COOH + C_6H_5NH_2 \xrightarrow[H_2O,\ 45\ ^\circ C]{surfactant} C_{11}H_{23}CONHC_6H_5$$

(Eq. 2)

With the former surfactant and under identical conditions, a stable emulsion was formed. Yet, this stability was water content dependent as stated below. The emulsion droplets, having a hydrophobic core, can prevent the hydrolytic decomposition of the formed dodecanilide. Therefore, the equilibrium position for the hydrophobic substrate would lie at the product side because as soon as the water molecule was formed, it would have been expelled from the core of the droplets as depicted in Figure 1 [2]. The yield was moderate, about 37% (Table 2).

For a molar ratio [aniline]/[dodecanoic acid] of 1.7/1 and 0.05 equivalent of SDS, volume of water lower than 1.5 mL and higher than 3 mL afforded unstable emulsion and lower yields; a highly stable emulsion was observed with 1.5 mL of water. On the other hand, for amounts of aniline lower than 1.7 mmoles, the stability emulsion decreased. Study of the SDS amount on the system and the yield revealed that an equivalent of 0.05 engendered higher stability of the emulsion state with higher yield, for the above optimal conditions; lower equivalents gave unstable emulsion and greater ones provoked gel formation. Effect of reaction temperature on the results showed that the formation of dodecanilide, under the optimal conditions cited above, was very slow (24 h) at a temperature of 30 °C, occurred after 4 h for 45 °C, and finally 2 h for 60 °C. However, only at a temperature of 45 °C, the emulsion was very stable and the yield was greater.

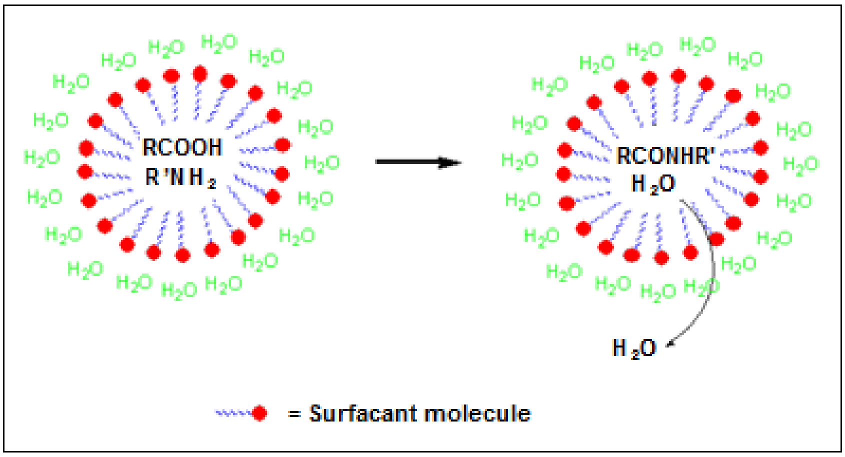


**Figure 1**: Picture of the reaction within a micellar system

However, with CTAB surfactant, two separate phases were observed: an oily layer on top of a milky suspension layer. This phenomenon suggested the instability of the formed emulsion. Increasing the concentration of CTAB up to 20 mol % did not enhance the stability, although the suspension became milkier. Dodecanilide was isolated in this case in almost the same yield (35%) as with SDS (Table 2).

**Table2**: Effect of surfactants on the formation of fatty dodecanilide in water.

| Entry | Surfactant (mol %) | Yield (%) |
|---|---|---|
| 1 | 0 | 5.25 |
| 2 | SDS (5) | 37 |
| 3 | CTAB (20) | 35 |

### 2.4 *Surfactant/Acid Combined*

In view of improving the outcomes of the reaction, acid catalysis coupled with a surfactive medium was applied to the reaction in water under the same reaction conditions. For this matter, SDS/HCl and SDS/lanthanide triflate systems, and *p*-dodecylbenzenesulfonic acid (DBSA) as a surfactant-type Brønstëd acid catalyst which was expected to behave both as an acid and as a surfactant, were attempted. The results are gathered in Tables 3 and 4.

The results shown in Table 3 shed light on the catalytic supremacy of DBSA as promoting the best yield, nearly 60%; with the former system, only 33% yield was gained. This is probably due to the formation of hydrophobic colloidal particles in water and the strong acidity of DBSA; in the presence of the latter, the reaction mixture became turbid, and the formation of these colloidal dispersions is a characteristic feature for the present reaction system [24, 32]. Surprisingly, no synergetic effect was observed when combining SDS with DBSA, hinting at the suppressing catalytic effect of SDS.

**Table3**: Effect of Brønstëd acids on the formation of fatty dodecanilide in water.

| Entry | Catalyst (mol. %) | Yield (%) |
|---|---|---|
| 1 | SDS(5)+ HCl (5) | 33.50 |
| 2 | DBSA(10) | 58.00 |
| 3 | SDS(5) +DBSA (10) | 01.24 |

The use of Lewis acids as catalysts in organic reactions requires anhydrous conditions because of their water-sensitive nature. Yet, some metal salts as rare earth metal triflates can be used as water-stable Lewis acids [26]. Kobayashi *et al.* found that lanthanide triflates, Ln(OTf)$_3$, act as strong Lewis acid because of their hard character and have strong affinity toward carbonyl oxygens [33].To avoid the use of organic solvents, these authors developed new water-borne synthetic methods, in which lanthanide triflates catalyze reaction in water without using any organic solvent, but with the aid of a surfactant such as SDS [5].

In the present work, the reaction mixture separated in two phases when run in the presence of Ln(OTf)$_3$-SDS system. Three Ln(OTf)$_3$ were tested: Sc(OTf)$_3$, La(OTf)$_3$, Yb(OTf)$_3$. Dodecanilide was isolated from the organic layer in low to moderate yields as shown in Table 4. Sc(OTf)$_3$ afforded the highest yield, a result that is in tune with Kobayashi's work [5].

**Table 4**: Effect of SDS/Ln(OTf)$_3$ system on the formation of dodecanilide in water. [SDS] = 5 mol.%

| Entry | Ln(OTf)$_3$ (10 mol.%) | Yield (%) |
|---|---|---|
| 1 | Yb(OTf)$_3$ | 21.10 |
| 2 | La(OTf)$_3$ | 30.50 |
| 3 | Sc(OTf)$_3$ | 38.20 |

## Conclusion

Solvent-free strategy favors higher yields of fatty alkanilides but under higher temperatures. Aqueous environment with milder reaction conditions would afford anilides in low to moderate yields. Stability of the micellar medium, a prerequisite for promoting higher yields, is affected by a number of conditions, namely the molar ratio of reactants, the volume of water used, the amount of emulsifying agent, the reaction time and temperature. In the 'surfactant/acid combined' system, sodium dodecylsulfate (SDS) seemingly desactivate the catalytic capacity of *p*-dodecylbenzenesulfonic acid (DBSA). Acid surfactants such as DBSA and Ln(OTf)$_3$/SDS system such as Sc(OTf)$_3$/SDS promoted acceptable yields. The water-borne synthesis of alkanilides in the presence of surfactants would be of a special interest for environmentally friendly industry.

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