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An eco-friendly protocol for synthesis of thiourea derivatives: 1-benzoyl-3-benzylguanidine and 1-benzoyl-3-benzyl-*O*-ethylisourea. A possible non-purely thermal microwave assisted reaction

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Abstract—1-Benzoyl-3-benzylguanidine and 1-benzoyl-3-benzyl-*O*-ethylisourea were synthesized in good yields (68 and 76%, respectively) from 1-benzoyl-3-benzylthiourea and benzoyl-ethylthiocarbamate in dry media conditions using $KF–Al_2O_3$ under microwave irradiation. Strong nucleophilic amines promoted the sulfur elimination by attack on the thiocarbonyl group in both thiourea and thiocarbamates to afford guanidines and isourea, respectively. Transesterification products were obtained from *p*-TsOH catalyzed reaction of thiocarbamate with alcohols under MW-solvent-free conditions. Very important non-purely thermal MW specific effects were evidenced and attributed to stabilization by coulombic interactions between materials and waves.

1. Introduction

Substituted guanidines are interesting compounds that are utilized in medicine[1–3] as analgesic[4] and antihypertensive[5] compounds. In analytical chemistry, guanidines have been used as extraction agents for periodate ions.[6] In addition, guanidines are also useful in organic synthesis.[7–9]

The substituents on the guanidine group influence the physico-chemical properties and biological activities of these molecules. For instance, the introduction of an acyl group on one of the guanidine nitrogen atoms markedly reduces the guanidine basicity.[10]

Several methods have been reported for the preparation of guanidines in solution.[11–15] Recently, the conversion of *N*-benzoylthioureas into guanidines has been disclosed in good yields using $Bi(NO_3)_3 \cdot 5H_2O$ as a catalyst.[16] Solid-phase syntheses of trisubstituted guanidines[17] and *N*-acyl-*N*′-carbamoylguanidines[18] have been also reported.

Microwave (MW) activation has been used for guanidines preparation under both dry[19] and in solution.[20] However, in the first case, several reaction steps and the use of the very toxic isocyanates were required, whereas the second work described the use of non-volatile solvents and hazardous diamines as guanidine precursors at high temperatures (> 150 °C).

Alkylisoureas like **2a** are hydantoin derivatives. This class of compounds has been used as anti-convulsants in the treatment of epilepsy and heart arrhythmia.[21–22] On the other hand, alkylisoureas are useful materials for ester preparation by O-alkylation of carboxylic acids.[23] The first synthesis of hydantoins was described as early as 1911, using KOH–EtOH, which resulted in very low yields.[24] Recently, the synthesis of phenytoin, a hydantoin analogue, has also been reported by using MW activation.[25] Classical preparations of alkylisoureas require of carbodiimides as starting materials and long reaction times.[26] Improvements were introduced by using of the solid supported carbodiimides[27] and microwave irradiation.[26]

The use of MW technology together with solvent-free conditions allows improvements in yields, selectivity and

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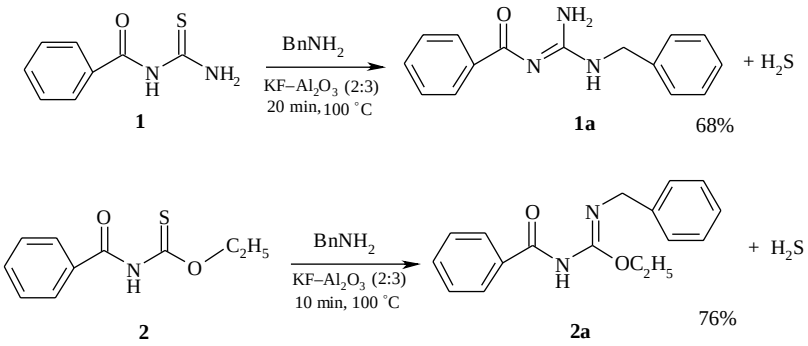
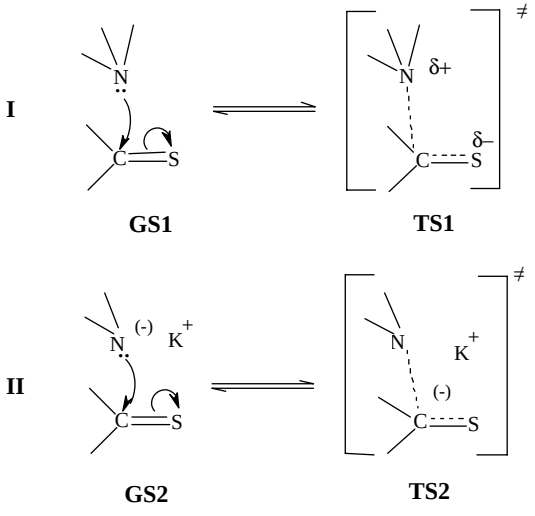


Scheme 1. Synthesis of 1-benzoyl-3-benzylguanidine **1a** and 1-benzoyl-3-benzyl-*O*-ethylisourea **2a**.

work up, with shortened reaction times when compared with classical methods.[28–34]

This work describes the synthesis of 1-benzoyl-3-benzylguanidine **1a** and 1-benzoyl-3-benzyl-*O*-ethylisourea **2a** from the corresponding thiourea derivatives **1** and **2**, respectively, under MW irradiation under solvent-free conditions using potassium fluoride impregnated onto alumina as the catalyst (Scheme 1) (Scheme 2). A special aim of the present work is the reaction of thiocarbamates **2** with alcohols to yield the transesterification products **2b** and **2c** (Scheme 3), which constitutes an extension of the previous non-classical synthesis of thiourea related compounds.[35–36]



Scheme 2. Rate determining steps in the mechanism of amine addition to the thiocarbonyl functionality in neutral **I** or basic **II** medium.

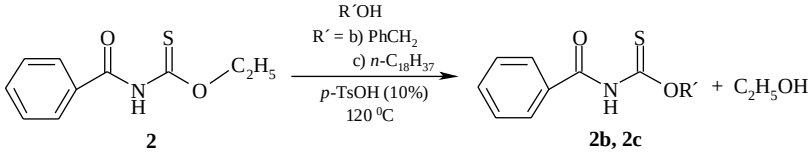
2. Results and discussions

Microwave experiments were carried out in open vessels with an efficient mechanical stirring (which avoids all problems of non-homogeneity in temperature). Several inorganic supports were tested in order to achieve the best product yields. The support/substrate relative amounts were previously optimized. Experiments were replicated to ensure reproducibility. In order to check the possible intervention of the specific non-purely thermal MW effects,[37,38] the same reactions were performed using an oil bath controlled using a thermostat under similar conditions. Table 1 shows the results obtained for the synthesis of **1a** or/and **2a**. A single-mode focused MW reactor was used to ensure a higher reproducibility and a better control of the reaction parameters (power, temperature).

The best yields (68 and 76% for guanidine **1a** and alkylisourea **2a**, respectively) were obtained using KF impregnated on alumina. Experiments performed at higher output power and for longer exposure times were unsuccessful (higher yields were not observed and decomposition products were detected by TLC analysis). No reaction was observed below 100 °C. Figure 1 showed the profiles of rises in temperature and emitted power during microwave assisted synthesis of **1a**. An emitted MW power value of 60 W was sufficient to maintain a constant temperature of 120 °C.

In all cases, it has been found that reactions proceed with considerable lower yields under similar temperature conditions by conventional heating demonstrating that the effect of MW is evidently not only purely thermal.

Microwaves are electromagnetic waves generated by an alternating electric field of high frequency. The energy



Scheme 3. Acid-catalyzed transesterification of **2** under MW irradiation without solvent.

Table 1. Synthesis of **1a** and **2a** under MW irradiation by reacting **1** and **2** with benzylamine

Reagent (2 mmol)	Support[a]	t (min)	T (°C)	Product	Activation mode	Yield (%)[b]
					Δ[c]	MW
1	No support	20	120		—	51
		20	100	**1a**	<10	168
	$KF–Al_2O_3$	15	120		—	59
2	No support	3	100		<10	40
		5	120		21	52
	$KF–Al_2O_3$	3	100	**2a**	17	67
		10	100		—	76

[a] $KF–Al_2O_3$=3/2 w/w.
[b] Yields of isolated products.
[c] Conventional heating controlled using a thermostat oil bath wash under similar conditions.

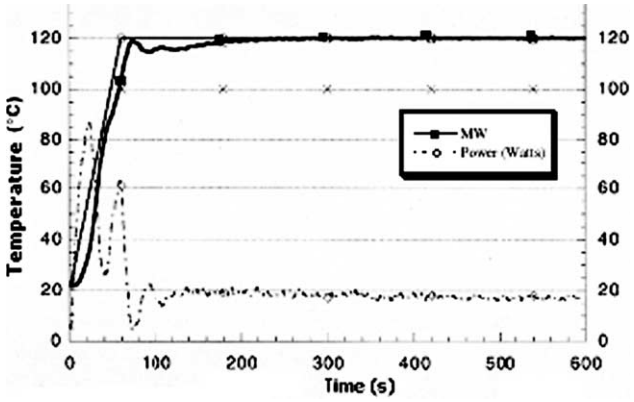


Figure 1. Profile of rise in temperature for the MW assisted solvent-free synthesis of **1a**.

associated with a MW photon (1 J mol^{-1} by application of Planck's law: $E=h\nu$ with $\nu=2450$ MHz) is far too small to induce any excitation of molecules. It can, however, induce thermal effects due to some internal friction between polar molecules during their changes in orientation with each alternation of the electric field. In addition, they can induce some electrostatic interactions with polar materials by dipole–dipole interactions, rather similar to the behavior of a dipolar solvent.[39]

By analogy and extension of the interpretation of solvent effects, the reactions can be facilitated when there is an increase of the polarity of the system during the progress of the reaction between the ground state and the transition state. An increase in MW efficiency could result therefore from both thermal effects (which provide adequate thermal energy) and specific polar electrostatic (non-purely thermal) effects.[34]

The specific MW effects we have evidenced here are consistent with the consideration of the mechanism and with the assumption that MW effects are increased when the polarity of a system is increased during the progress of the reaction (Scheme 2): [37,38,40,41]

– For the support (base)-free reaction, the rate determining step is the nucleophilic attack of the amine on thiocarbonyl moiety **I**. One can thus expect an important MW effect due to the enhancement of polarity of the system provided by the dipolar transition state TS1 when compared to neutral ground state GS1.[37–42]

– For the base-activated reaction (i.e., of KF–alumina), the enhancement of polarity of the system during the reaction is provided by ionic dissociation of the ion pairs from GS2 toward TS2 **II**, which is more polar due to the negative charge delocalization.[43]

In both cases, the most important phenomenon is the stabilization of the transition states by dipole–dipole electrostatic interactions with the electric field, which therefore could be responsible for an enhancement of reactivity by a decrease of the activation energy (Scheme 2).

A special interest lies in the reaction of **2** with $BnNH_2$ yielding the corresponding **2a** with H_2S elimination. On the other hand, when catalyzed by *p*-TsOH, the reaction of compound **2** with alcohols leads to the transesterification product, without sulfur elimination. Thus, two other thiocarbamates **2b** and **2c** were synthesized through transterification of **2** (Scheme 3) in order to confirm the reactivity of thiocarbamates toward molecules with different nucleophilic strength. This reaction has afforded the corresponding thiocarbamates in high yields and short reaction times (Table 2). Therefore, the present microwave assisted-acid catalyzed transesterification of thiocarbamate was more efficient than the reported classical procedure.[44]

The main results for thiocarbamates transesterification are displayed in Table 2.

The dielectric environment during MW-assisted transesterification of **2** aid the formation of polar intermediates formed during the acid-catalyzed transesterification reaction. The rapid microwave induced volatilization of the leaving alcohol (ethanol) molecule would shift the equilibrium favorably to formation of the transesterification product.[45]

Reactions carried out without acid catalysis showed low yields of the transesterification product presumably due the elimination of the ethanol molecule and formation of the isothiocyanate occurring before the nucleophilic attack of the benzyl alcohol (reactions 1–4 in Table 2). This thermal process seems to be more rapid under microwaves irradiation (reactions 1–2 in Table 2) and showed a strong dependence on the exposition time (reactions 3–4 in Table 2) yielding decomposition at 20 and 180 min of irradiation. When the reaction was conducted under classical heating (120 °C) for 24 h a 61% of **2b** was obtained together some decomposition products. This

Table 2. Results of synthesis of thiocarbamates **2b** and **2c** by reaction of **2** (2 mmol) with benzyl and octadecyl alcohol under MW irradiation

R′OH (mmol)	Catalyst (mmol)	Time (min)	*T* (°C)	MW, yield (%)	Δ, Yield (%)
BnOH (2)	—	10	100	52	—
	—	10	120	64	25
	—	20	100	—[a]	28
	—	180	120	—	52[b]
	0.2	10	100	64	—
	1	5	120	70	45
	1	10	120	88	50
BnOH (**4**)	1	**10**	**120**	**94**	**48**
n-$C_{18}H_{37}OH$ (2)	—	20	120	61	27
***n*-$C_{18}H_{37}OH$ (2)**[c]	1	**20**	**120**	**85**	**41**

Comparison with classical heating (Δ).
[a] Decomposition products.
[b] Δ 24 h → 120 °C, 61%.
[c] Higher alcohol amounts did not affect the product yield.

behavior will be carefully investigated and the results will be opportunely communicated.

3. Conclusion

In conclusion, we describe herein an efficient and eco-friendly protocol for the synthesis of 1,3-substituted guanidines, alkylisoureas and thiocarbamates in good yields. Special interests lie in the procedures for preparation of guanidines and alkylisoureas, where a non-purely thermal effect of the microwave irradiation is evidenced. In addition, transesterification of ethyl thiocarbamate with benzyl and octadecyl alcohols give the corresponding transesterificated products, resulting in a useful procedure toward other thiocarbamates.

4. Experimental

4.1. General methods

Reactions were performed in a Prolabo monomode reactor Synthewave™ 402 device.[30] The temperature was measured during the reaction by an optical fiber introduced inside the stirrer or by infrared detection, which indicates the surface temperature after previous calibration of emissivity in each case with an optical fiber (FTI-10 device from Fiso). All reactions were carried out in a cylindrical Pyrex tube with mechanical stirring to establish homogeneity in temperature. The emitted power was monitored (between 15 and 300 W) to maintain a constant temperature.

Melting points were obtained using Electrothermal 9100 apparatus. ^{1}H NMR spectra were recorded on a Bruker AC spectrometer at 250 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 62 MHz. Chemical shifts are expressed in δ (ppm) using tetramethylsilane (TMS), which was used as an internal standard. IR spectra (ν_{max} cm^{-1}) were recorded on Bruker IR S48 using KBr pellets. EI mass (70 eV) spectra were obtained on HP5989A spectrometers. The reactions were followed by silica-gel plates (Merck $60F_{250}$) TLC performed using chloroform–ethyl acetate (8/2) as the eluent. All the chemicals were purchased from Aldrich and used as received.

4.2. Typical procedure for synthesis of 1a and 2a from benzoylthiourea 1 and thiocarbamate 2 under microwave irradiation

Benzoylthiourea **1** (2 mmol) or ethyl benzoylthiocarbamate **2** was dissolved in acetone. An equimolar amount of benzylamine was added and the mixtures were smoothly mixed with 1 g of KF–alumina (3/2). The solvent was removed under reduced pressure. The resulting mixture was placed into a Pyrex-glass open vessel and irradiated in the monomode MW reactor for the reaction times and temperatures as indicated in Table 1. The products were extracted from the support with acetone and precipitated using ice water.

Benzoylthiourea **1** and ethyl-*N*-benzoylthiocarbamate **2** were obtained according to the standard procedure previously reported in the literature.[35–36]

4.3. Typical procedure for microwave assisted transesterification of thiocarbamate 2. Synthesis of 2b and 2c

Equimolar amounts (2 mmol) of alcohol and ethyl benzoylthiocarbamate **2** were dissolved in acetone. The solvent was removed under reduced pressure. 1 mmol of *p*-TsOH was added slowly. The resulting mixture was placed into a Pyrex-glass open vessel and irradiated in a monomode MW reactor for reaction times and temperatures as indicated in Table 2. The reaction mixture was extracted with petroleum ether (bp 60 °C)–cyclohexane (1/1), yielding a white compound. The product was dissolved in dichloromethane and filtered to separate insoluble *p*-TsOH. After solvent evaporation, the white precipitate was purified by a column silica gel chromatography using toluene–methanol (5/1) as eluent.

4.4. Comparison between microwave activation and conventional heating for compounds 1a, 2a–c

In order to compare the results of MW irradiation versus conventional heating (Δ), the same reactions were performed inside a preheated thermostated oil bath at the same temperature as under MW irradiation. The reaction was achieved for the same reaction time. The temperature was controlled with the same optical fiber thermometer as for the calibration of MW's emissivity and the profile of temperature rise was adjusted to be similar to that registered

under microwave irradiation. The treatment and analysis remained identical.

4.5. Spectroscopic data

4.5.1. *N*-Benzoylthiourea 1. Yield 73% (from acetone–H_2O). Mp 178–179 °C; lit.[46] mp 186–187 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=7.92–7.46 (m, 5H), 9.7 (d, 2H), 11.25 (s, 1H); ^{13}C NMR (DMSO-d_6, 62 MHz) δ=128.4 (CH), 129.4 (CH), 131.8 (CH), 134.9 (C_{ipso}), 161.9 (CO), 179.4 (CS); FT-IR (KBr): ν_{max} (cm^{-1})=3205, 3100, 1680, 1600, 1550, 1390; EI-MS *m/z*: 181.2 $(M+H)^+$.

4.5.2. *N*-Benzoyl-ethylthiocarbamate 2. Yield 64% (from acetone–H_2O). Mp 59–61 °C; lit.[47] 65–74 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=1.40 (t, 3H), 4.60 (m, 2H), 7.45–7.90 (m, 5H), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ=13.6 (CH_3), 69.2 (CH_2), 127.6 (CH), 128.8 (CH), 132.8 (CH), 133.0 (C_{ipso}), 162.8 (CO), 189.3 (CS); FT-IR (KBr): ν_{max} (cm^{-1})=3257, 3100, 1697, 1599, 1522, 1295; EI-MS *m/z*: 210.2 $(M+H)^+$.

4.5.3. 1-Benzoyl-3-benzylguanidine 1a. Mp 184–185 °C; lit.[48] 186–190 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=4.42 (m, 2H, broad signal), 4.45 (d, 2H), 7.23–8.22 (m, 10H), 9.1 (t, 1H); ^{13}C NMR (DMSO-d_6, 62 MHz) δ=49.2 (CH_2), 127.1 (CH), 127.2 (CH), 127.3 (CH), 127.4 (CH), 128.2 (CH), 128.3 (C_{ipso}), 133.0 (C_{ipso}), 136.0 (CH), 161.8 (CO), 177.2 (CN); FT-IR (KBr): ν_{max} (cm^{-1})=3234, 3105, 1679, 1590, 1498; EI-MS *m/z*: 252.1 $(M+H)^+$.

4.5.4. 1-Benzoyl-3-benzyl-*O*-ethylisourea 2a. Mp 159–160 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=1.36 (t, 3H), 4.51 (s, 2H), 4.52 (m, 2H), 7.23–8.24 (m, 10H), 10.3 (s, 1H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ=14.4 (CH_3), 44.8 (CH_2), 63.7 (CH_2), 127.0 (CH), 127.3 (CH), 127.6 (CH), 128.1 (CH), 129.1 (CH), 131.1 (CH), 134.0 (C_{ipso}), 134.2 (C_{ipso}), 162.8 (CO), 177.6 (CN); FT-IR (KBr): ν_{max} (cm^{-1})= 3234, 3105, 1679, 1612, 1590, 1498; EI-MS *m/z*: 283.1 $(M+H)^+$.

4.5.5. *N*-Benzoyl-benzylthiocarbamate 2b. Mp 104–106 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=5.62 (s, 2H), 7.25–7.83 (m, 10H), 9.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 62 MHz): δ=74.2 (CH_2), 127.1 (CH), 127.3 (CH), 127.7 (CH), 128.3 (CH), 129.0 (CH), 131.1 (C_{ipso}), 137.4 (C_{ipso} and CH), 188.9 (CS), 162.8 (CO); FT-IR (KBr): ν_{max} (cm^{-1})=3314, 3073, 1693, 1601, 1519, 1456, 1377; EI-MS *m/z*: 272.2 $(M+H)^+$.

4.5.6. *N*-Benzoyl-stearylthiocarbamate 2c. Mp 67.5–68.5 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=0.9 (m, 3H), 1.0–1.5 (m, 30H), 1.8 (m, 2H), 4.6 (m, 2H), 7.4–7.9 (m, 5H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 62 MHz): δ=14.1 (CH_3), 22.7 (CH_2), 31.9 (CH_2), 31.9 (CH_2), 73.8 (OCH_2), 127.7 (CH), 129.0 (CH), 133.1 (C_{ipso} and CH), 162.7 (CO), 189.7 (CS); FT-IR (KBr): ν_{max} (cm^{-1})=3256, 3021, 1704, 1604, 1538, 1300. Anal. Calcd for $C_{26}H_{43}NO_2S$ (433.54): C, 72.02; H, 9.98; N, 3.22. Found: C, 72.12; H, 9.88; N, 3.17.

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