Pergamon

Tetrahedron Letters 41 (2000) 1753–1756

TETRAHEDRON LETTERS

Synthesis of 1-benzoyl-3-alkylthioureas by transamidation under microwave in dry media†

Heiddy Márquez,[a] Eduardo R. Pérez,[a] Ana M. Plutín,[a] Margarita Morales [a] and André Loupy [b,*]

[a]*Laboratorio de Síntesis Orgánica, Facultad de Química, Universidad de La Habana, 10400, La Habana, Cuba*
[b]*Laboratoire des Réactions Sélectives sur Supports, ICMO, UMR 8615, Bât. 410, Université Paris-Sud, 91405 Orsay Cédex, France*

Received 19 November 1999; accepted 24 December 1999

Abstract

1-Benzoyl-3,3-diethylthiourea was transamidated with several amines to the corresponding 1-benzoyl-3-alkylthioureas in open vessels under microwave irradiation using a domestic oven. The syntheses were performed in solvent-free conditions on potassium fluoride impregnated alumina. Yields were dramatically improved in comparison with classical heating under the same conditions.

The chemistry of organic sulfur compounds such as thioureas, has been developed with increasing interest due to their important biological activities.[1,2] Classical methods to obtain thiourea-like compounds show several difficulties involving very toxic isothiocyanates and some undesirable effects of the solvents. Also these reactions are classically carried out under refluxing conditions for long durations frequently with some decomposition of the reagents or products.

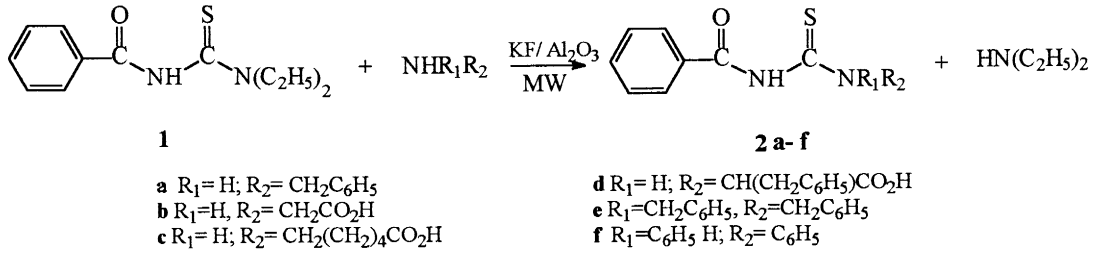
During the last years, 'non-classical' methods have been developed in organic synthesis in order to improve both yields, selectivity and experimental conditions.[3] Especially the use of microwave technology in conjunction with the use of solvent-free conditions allows expeditious and efficient procedures in organic synthesis.[4–7] The salient features of these high yield protocols lie in enhanced reaction rates, higher purity of products and very simplified ease of manipulation and work-up. They clearly constitute an eco-friendly 'green' approach.[8]

In the present work, we report the synthesis of 1-benzoyl-3-alkylthioureas **2** by a transamidation procedure under microwave irradiation in dry media using several inorganic solid supports as a convenient and efficient way to prepare these classes of organic compounds (Scheme 1).

* Corresponding author. Fax: 33-1-69-15-46-79; e-mail: aloupy@icmo.u-psud.fr (A. Loupy)

† This paper is dedicated to the memory of Professor Yolanda Rodríguez Esteva (Universidad de La Habana).

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00047-2



1

2 a- f

a R_1= H; R_2= $CH_2C_6H_5$
b R_1=H, R_2= CH_2CO_2H
c R_1= H; R_2= $CH_2(CH_2)_4CO_2H$
d R_1= H; R_2= $CH(CH_2C_6H_5)CO_2H$
e R_1=$CH_2C_6H_5$, R_2=$CH_2C_6H_5$
f R_1=C_6H_5 H; R_2= C_6H_5

Scheme 1.

Microwave experiments were carried out testing several inorganic supports in order to achieve the best yields avoiding decomposition of both reagents and products. The support/substrate relative amounts were previously optimized. Experiments were replicated in order to ensure reproducibility. Final temperatures were measured immediately after the reaction using a glass thermometer. In order to check the possible intervention of specific (non-purely thermal) microwave effects, the reactions were also carried out using a thermostated oil bath at 95–100°C with the same reaction medium and conditions as under microwave.

Table 1 shows the most significant results obtained in the synthesis of **2a** (R_1=H, R_2=$CH_2C_6H_5$) under microwave irradiation using several supports in dry media. The best yield (81% in isolated product) was reached using potassium fluoride impregnated on alumina as support.[9] Experiments performed at higher output power and for longer exposure times were unsuccessful (no higher yields were observed and more decomposition products were detected by TLC analysis of the reaction mixtures). Yields were determined from isolated products.[10]

Table 1
Synthesis of **2a** under microwaves (power 560 W) using several inorganic supports (1 g), by reacting equivalent amounts of **1** and benzylamine (2 mmol)

Support	Reaction time (min)	Temperature (°C)	Yield (%)
No support	5	60	< 10
Al_2O_3-KF	*2*	*100*	*81*[a]
Neutral Al_2O_3	3	93	59
Basic Al_2O_3	3	95	64
Acidic Al_2O_3 [b]	4	98	46
ZnO	4	96	52
K10	4	100	20
KSF	5	98	43

a) Yield is 79 % by scaling up to 20 mmoles of each reactant under the same conditions
b) Previously calcinated at 500 °C

Experiments performed in a thermostated oil bath lead to low yields as shown in Table 2, with the starting materials and decomposition products as the complements.

The results shown in Table 2 allow us to propose the microwave–dry media coupled method with potassium fluoride impregnated alumina as an efficient and selective technique to prepare the 1-benzoyl-3-alkyl thioureas **2a**–**f** by the transamidation reaction. A strong specific non-thermal microwave effect was evidenced as yields were incremented from 4–35% to 69–90%.

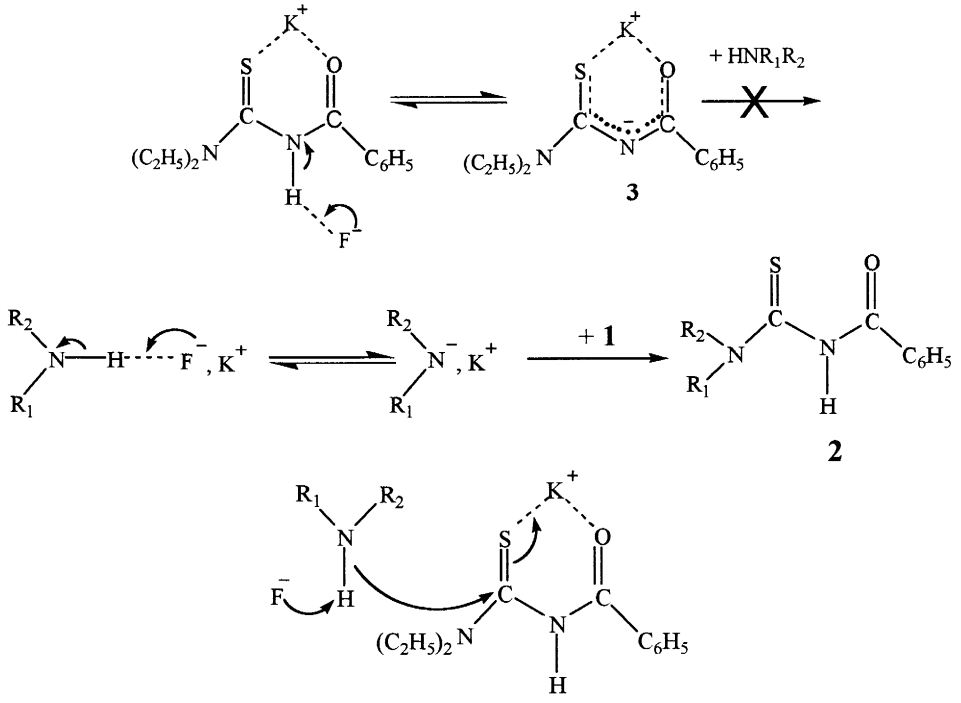
Table 2
Comparison between microwave and oil bath (95–100°C) for synthesis of **2a–f**

Comp.	Microwave		Oil bath (%)		m.p. (°C)	
	(min)	(%)	(60 min)	(300 min)		Lit
2a	2	**81**	15	35	117-120	118-120 [11]
2b	4	**86**	9	13	198-200	202 [12]
2c	3	**90**	10	14	125-127	127.5-128 [12]
2d	3.5	**78**	traces	8	157-160	158-159 [12]
2e	4	**83**	traces	4	136-138	137-138 [11]
2f	4.5	**69**	traces	6	204-206	205-206 [11]

We could suggest two explanations for the improvement achieved with this method both on product yields and reaction selectivity:

(i) The more polar charged intermediates could have a strong microwave absorption with a consequent rise of temperature which accelerates the formation of very polar and volatile diethylamine (bp=55°C) and also avoids the reversibility of the process.

(ii) The second effect could be the strong basicity of KF-alumina. Whereas benzoylthiourea **1** is more acidic (generating thus the polydentate anion **3**), its ionization does not lead to any reaction. On the other hand, ionization of the amines (or at least weakening of N–H bond due to hydrogen bonding) can take place and then induce activation of amine nucleophilicity[9,13] (Scheme 2).



Scheme 2.

In short, we have described an alternative efficient method to obtain 1-benzoyl-3-alkyl thioureas which does not present the selectivity problems associated with direct alkylations of the benzoylthioureas.[14]

References

1. Ramadas, K.; Suresh, G.; Janarthanan, N. *Pestic. Sci.* **1998**, *52*, 145.
2. Liu, S.Q.; Tang, C.; Ho, B. *J. Med. Chem.* **1998**, *41*, 4693.
3. *Chemistry under extreme or non-classical conditions*; Van Eldik, R.; Hubbard, C. D., Eds.; J. Wiley & Sons: New York, 1996.
4. Bram, G.; Loupy, A.; Villemin, D. In *Solid Supports and Catalysts in Organic Synthesis*; Smith, K., Ed.; Ellis Horwood, PTR Prentice Hall: Chichester, **1992**, 302.
5. Pérez, E. R.; Marrero, A. L.; Pérez, R.; Autié, M. A. *Tetrahedron Lett.* **1995**, *36*, 1779.
6. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213.
7. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A.; *Tetrahedron* **1999**, *55*, 10851.
8. Varma, R. S. *Green Chemistry* **1999**, *1*, 43.
9. Clark, J. M. *Chem. Rev*. **1980**, *80*, 429.
10. Typical procedure: 1-benzoyl-3,3-diethylthiourea **1** (2 mmol) was dissolved in acetone. An equimolar amount of the indicated amines were then added and the mixture then smoothly mixed with 1 g of KF-alumina. The solvent was removed under reduced pressure. The resulting mixture was placed into a Pyrex-glass open vessel and irradiated in a microwave domestic oven at 560 W for the times and final temperatures as indicated in Tables 1 and 2. The products were extracted from the support with acetone and precipitated with ice water.
11. Plutín, A. M. M.Sc. Thesis *Estudio de la alquilación de un sistema polidentado: 1-aciltioureas—3,3-disustituidas*; University of Havana, Cuba, 1997.
12. Elmore, D. T.; Ogle, J. R. *J. Chem. Soc.* **1958**, 1141.
13. Villemin, D.; Ricard, M. *Tetrahedron Lett*. **1984**, *25*, 1059.
14. Rodríguez, Y.; Cardeñas, M.C.; Plutín, A. M.; Macías, A.; Del Bosque, J. R. *An. Quím.* **1995**, *91*, 696.