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An efficient one-step regiospecific synthesis of novel isoxazolines and isoxazoles of N-substituted saccharin derivatives through solvent-free microwave-assisted [3+2] cycloaddition

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Abstract—Novel isoxazolines and isoxazoles of N-substituted saccharin derivatives are synthesized in good yields by 1,3-dipolar cycloaddition of *N*-allyl or propargyl N-substituted saccharin with arylnitrile oxide under solvent-free microwave irradiation. In this process, the yields were significantly improved over conventional heating, without alteration of the selectivity. The regioselectivity as well as the nonthermal specific microwave effect are discussed.

There has been a gradual change from classical reaction conditions to more environmentally friendly routes.[1] This growth of green chemistry holds significant potential for reduction of the by-products and in waste production and lowering of energy costs. Microwave (MW) irradiation is now used in a lot of chemical transformations for the synthesis of various compounds.[2] The most evident improvements are reduced reaction time and cleaner reactions due to less side products. The intermolecular [3+2] cycloaddition reaction of arylnitrile oxides with various alkenes and alkynes represent an efficient and convergent method for the construction of isoxazoline and isoxazole rings.[3] Recently, our research was focused on the application of microwave activation in organic synthesis, particularly in 1,3-dipolar cycloaddition reaction. Carrying out reactions using solvent-free conditions and under microwave irradiation,[4] as opposed to conventional heating, has the advantage to increase the reaction rates because of the rapid core heating associated with microwaves and to a possible intervention of specific nonpurely thermal effects connected to medium polarities and mechanisms.[2]

Functionalized isoxazoline and isoxazole derivatives are active pharmacophores in several pharmacologically important molecules,[5] and are also useful intermediates for the synthesis of a wide variety of bioactive natural products.[6] Furthermore, the chemistry of saccharin and analogues has been a focus of intense research, due to their widespread occurrence in nature and their diversified biological activities.[7] N-Substituted saccharin derivatives have been extensively studied[7,8] but to the best of our knowledge there is no report of any incorporating an isoxazoline or isoxazole moiety. As part of our continued interest in the development of efficient methods for the synthesis of heterocyclic compounds of biological importance, we report herein a straightforward access to novel isoxazoline and isoxazole N-substituted saccharin derivatives via a one-pot 1,3-dipolar cycloaddition reaction, by using microwave activation under solvent-free conditions, in the presence of a simple and inexpensive catalyst (NCS/Al_2O_3). We have examined the 1,3-dipolar cycloaddition reactions of *N*-allyl and *N*-propargyl saccharin as dipolarophiles (Scheme 1)

Keywords: 1,3-Dipolar cycloaddition; Microwave activation; Regiocontrolled process; Arylnitrile oxide; Saccharin analogs.
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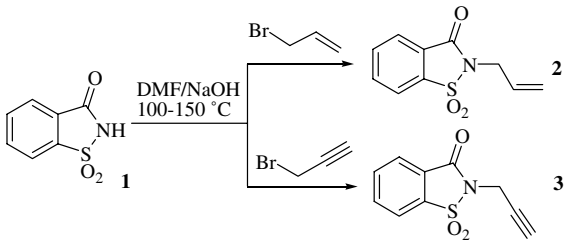
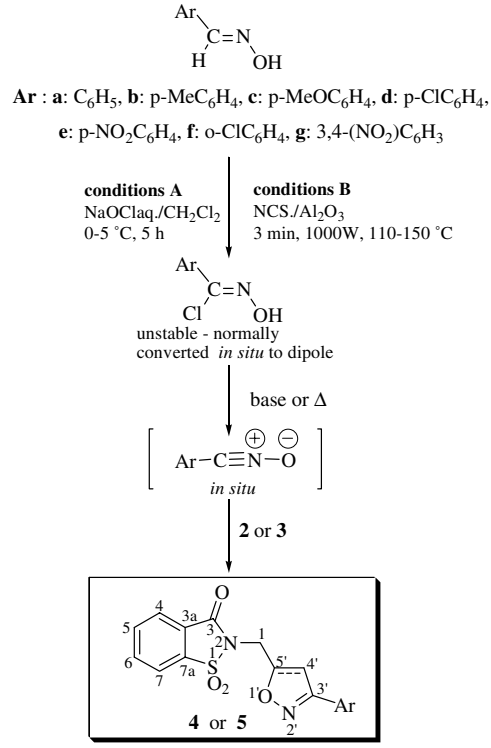


Scheme 1.

with arylnitrile oxides generated in situ from aromatic oximes precursors under conventional conditions (method A)[9] and microwave irradiation (method B), for the construction of isoxazoline and isoxazole rings **4** and **5**, respectively (Scheme 2).

First, the required dipolarophiles **2** and **3** were, respectively, prepared by N-allylation and N-propargylation of saccharin **1** (Scheme 1). The preparation of alkyl derivatives of saccharin has been previously reported using the sodium salt of saccharin with an alkyl halide. However, this procedure gave poor yields and generally required long reaction times, which is partially due to an inadequate solvent for this type of reaction.[10] Indeed, in our investigation, dimethylformamide was found to be an excellent solvent for the reaction of allyl and propargyl bromide with saccharin, in the presence of NaOH as the base. DMF is especially effective in this reaction for weakening the bromine–carbon bond. The *N*-allyl and *N*-propargyl saccharins **2** and **3** were obtained in 80% and 78% yield, respectively. The reaction is complete after 30 min when performed at a high temperature (100–150 °C). The obtained products **2** and **3** were characterized by spectral analysis and by comparison of their physical characteristics with those of authentic samples.



Scheme 2.

Dipolarophiles **2** and **3** were then treated with various arylnitrile oxides under usual conditions with aqueous NaOCl in methylene chloride (method A)[9] or under solvent-free microwave activation using NCS impregnated on alumina (method B). When reacting **2** or **3** with arylnitrile oxides using classical conditions, the dimerization of nitrile oxide into furoxan[9a] derivatives was the predominant reaction, lowering therefore the cycloaddition reaction yield. In our experiments, the furoxan dimer was isolated in the case of benzaldoxime.[9,11] Therefore, a search was made for the optimum conditions which would disfavor the competitive dimerization process. As shown in Table 1, when arylnitrile oxide was generated over 5 h, the cycloaddition reaction of arylnitrile oxide with dipolarophiles **2** or **3**, under conventional conditions, provided cycloadducts in low to moderate yields (14–45%, Table 1). The cycloadducts **4** or **5** were obtained with a regiocontrol as expected in the literature.[13]

Then, reactions under solvent-free conditions were conducted using a domestic microwave oven and dipolarophiles **2** or **3** as models. The duration of irradiation at maximal power (1000 W) was systematically varied to optimize the reaction conditions. Although manufacturers of microwave-heating apparatus have directed their research to make microwaves a safe source of heating, uncontrolled reaction conditions may result to undesirable effects.[4a] As depicted in Table 1, microwave irradiation for 3 min was found to be the best conditions for this type of cycloaddition. Thus, the cycloaddition involving dipolarophile **2** or **3** and arylnitrile oxides furnished the desired isoxazolines **4** or isoxazoles **5**, respectively, in high yields (81–95%), greatly improved when compared to the conventional method. Moreover, by using microwave activation, the reaction time was considerably decreased 100-fold. It is noteworthy that, in all cases TLC analysis indicated a complete conversion and formation of only one regioisomer without any post-isomerization compared to the classical conditions. The use of microwaves highly disfavored the dimerization process of arylnitrile oxides and this observation is rarely mentioned.[4,12]

As indicated by the results in Table 1 and Scheme 2, it appears that solvent-free and microwave activation on NCS/alumina is an efficient and more adaptable conditions for the synthesis of **4** and **5** like series. The structures of adducts **4** and **5** were confirmed through spectral analysis.

The IR absorptions of compound **4a** at $\nu_{max} = 1635\ cm^{-1}$ indicated the existence of the isoxazoline C=N group. The ^1H NMR spectrum of **4a** showed a multiplet centred at δ 5.23 ppm for the CH stereogenic centre and two doublets of doublets at δ 3.37 and δ 3.50 ppm for $C_{4'}HaHb$ protons. The N–CH_2 protons resonated as two doublets of doublets at δ 3.9 and 4.08 ppm. The aromatic proton exhibited a multiplet at δ 7.41–7.96 ppm. The ^{13}C NMR spectrum of **4a** exhibited a

Table 1. Formation of isoxazolines **4** and isoxazoles **5** under conventional and solvent-free conditions

Product	Conventional conditions		Solvent-free conditions			
	Time (h)	Yield[a] (%)	Time (min)	Temperature[c] (°C)	Yield[d] (%) [M_W]	Yield[e] (%) [triangle]
4a	5	20(79)[b]	3	130	91	0
4b	5	45	3	150	95	Trace
4c	5	40	3	120	93	Trace
4d	5	37	3	110	98	2
4e	5	30	3	130	92	3
4f	5	32	3	124	94	<2
4g	5	26	3	136	90	5
5a	5	12	3	120	81	0
5b	5	37	3	140	90	2
5c	5	32	3	112	88	3
5d	5	28	3	111	93	Trace
5e	5	25	3	119	87	Trace
5f	5	20	3	116	85	Trace
5g	5	14	3	130	83	4

[a] Yield of isolated product under stirring (method A): dipolarophiles **2** or **3** (1 mmol), arylaldoxime (1.2 mmol), aq NaOCl, CH_2Cl_2, −5 to 0 °C.
[b] Yield of the isolated furoxan (white crystalline solid, mp 114–116 °C).
[c] Evaluated temperature at the end of the reaction (infrared detection and a digital thermometric probe).
[d] Yield of isolated product under microwave (1000 W, 3 min) (method B): dipolarophiles **2** or **3** (1 mmol), arylaldoxime (1.2 mmol), NCS, Al_2O_3.
[e] Yield of isolated product obtained with classical heating (△) under same reaction conditions (3 min, final temperature, and atmospheric pressure) determined under microwave irradiation.

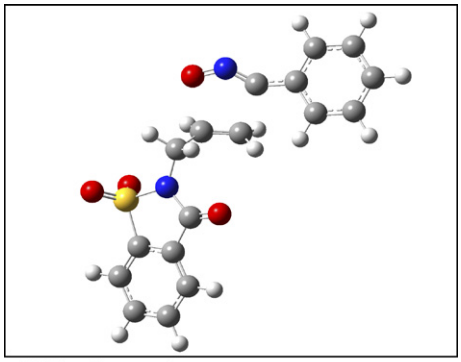
signal at 39.02 ppm corresponding to N–CH_2 carbon and two peaks at 41.94 and 77.53 ppm relative to $C_{4'}$ and $C_{5'}$ isoxazoline carbons. The C=N and carbonyl carbons $C_{3'}$ and C_3 resonated at 156.66 and 159.53 ppm, respectively. The structure of **4a** was further confirmed by mass spectrometry.

Similarly, the IR spectrum of compound **5a** showed an absorption at $\nu_{max} = 1611\ cm^{-1}$ due to the isoxazole C=N bond. The ^1H NMR spectrum of **5a** showed a singlet at δ 5.08 ppm for the N–CH_2 protons. The C_4–H isoxazole proton resonated as a sharp singlet at δ 6.68 ppm, and the aromatic proton as a multiplet at δ 7.42–8.13 ppm. The ^{13}C NMR spectrum of **5a** showed one signal at δ 33.88 ppm for the N–CH_2 carbon and two peaks at δ 102.39 and 162.93 ppm for the two characteristic isoxazole carbons C_4 and $C_{5'}$, respectively. The C=N and carbonyl carbons $C_{3'}$ and C_3 resonated at δ 158.65 and 165.96 ppm, respectively. Mass spectrometry is also in accordance with the proposed structure for **5a**.

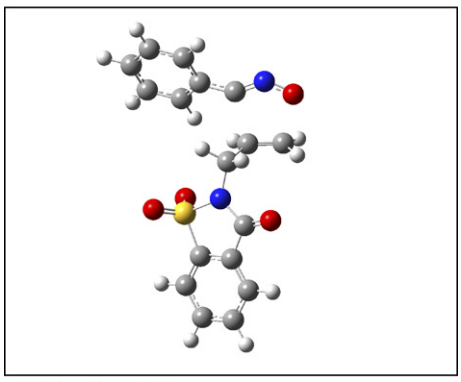
The regioselectivity observed is in accordance with the one normally found in nitrile oxide cycloaddition with terminal alkenes and alkynes.[13]

To get further insight into the factors responsible for the regioselectivity observed here, we performed calculations using the PM3 method[14] as implemented in the software available from ChemDraw 3D, version 4.0. We have thus checked the values of standard enthalpy formations ΔH_f^0 of final products **4a** and **6a** as well as of starting materials **2** and phenylnitrile oxide. After full geometry optimizations, the two possible transition states were considered leading to either **4a** or **6a** (Scheme 3). The main results are given in Table 2.

It is clear that the pathway leading to **4a** is favored, as the energy of activation is lower by 0.86 kcal/mol when compared to the other transition states. Otherwise, when considering the structure of **2a**, the charge densities (−0.17 and 0.18) and the atomic coefficients in π* orbital (−0.47 and −0.48), respectively, on the two carbon atoms of the double bond, one cannot predict any difference in the two attacks. One can finally assume that the preference for attack leading to **4a** is connected simply to the steric control of the reaction.



TS leading to **4a**



TS leading to **6a**

Scheme 3. The two possible transition states for the cycloaddition of phenylnitrile oxide and allyl saccharin.

Table 2. PM3 calculations of reagents, products and transition states (TS)

	ΔH_f^{0a}	E act.[b]	μ[c]
Phenylnitrile oxide	55.57		2.57
Allyl saccharin **2**	−54.34		3.65
Cycloadduct **4a**	−27.40		6.97
Cycloadduct **6a**	−23.28		6.98
TS toward **4a**	37.44	36.21	4.83
TS toward **6a**	38.30	37.07	3.60

[a] Standard enthalpy formation in kcal/mol.
[b] Energy of activation in kcal/mol.
[c] Dipole moment in Debyes.

Finally, in order to check the possible intervention of specific (nonthermal) microwave effects,[2,15] the best results obtained under microwave irradiation were extrapolated to conventional heating by carrying out the reactions under similar conditions (time, temperature, pressure, and vessel). It was found that the reaction did not occur and the reactants remained unchanged even on extended reaction times (Table 1), thus suggesting that the effect of microwaves is not simply thermal.[2,16,17]

The nonthermal MW effects evidenced here can be easily explained by considering the evolution of polarities between ground state and transition state. The values of dipole moments as given in Table 2 clearly indicate that the polarity is significantly increased from starting materials toward transition state and even toward the final product. Indeed, as the polarity is enhanced with the reaction progress, the dipole–dipole stabilization with the electric field is increased and consequently a positive MW effect is expected.[2,17]

In conclusion, we have developed, by coupling solvent-free conditions and microwave assistance, a new, efficient and green method for the synthesis of novel isoxazoline and isoxazole N-substituted saccharins. The process involves regiospecific [3+2] cycloaddition between alkenes or alkynes and arylnitrile oxides. The biological activity and inhibitory effect of such analogues against human leukocyte elastase (HLE), cathepsin G (Cat G), and proteinase 3 (PR 3) is under examination.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.067.

References and notes

1. (a) Varma, R. S. *Tetrahedron* **2002**, *58*, 1235; (b) Tanaka, K. *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2003.
2. (a) Kappe, C. O.; Stadler, A. In *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH, Ed.; Weinheim: Germany, 2005; (b) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed., Wiley-VCH: Weinheim, Germany, 2006.
3. (a) Colinas, P. A.; Jäger, V.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2003**, *44*, 1071; (b) Giacomelli, G.; De Luca, L.; Porcheddu, A. *Tetrahedron* **2003**, *59*, 5437; (c) Das, B.; Holla, H.; Mahender, G.; Banerjee, J.; Reddy, M. R. *Tetrahedron Lett.* **2004**, *45*, 7347.
4. (a) Bougrin, K.; Loupy, A.; Soufiaoui, M. *J. Photochem. Photobiol. C. Photochem. Rev.* **2005**, *6*, 139; (b) Guerguez, R.; Bougrin, K.; El Akri, K.; Benhida, R. *Tetrahedron Lett.* **2006**, *47*, 4807; (c) Bougrin, K.; Soufiaoui, M.; Bashiardes, G. In *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006, Chapter 11.
5. (a) Wagner, E.; Becan, L.; Nowakowska, E. *Bioorg. Med. Chem.* **2004**, *12*, 265; (b) Pastor, J.; Alcázar, J.; Alvarez, R. M.; Andrés, J. I.; Cid, J. M.; De Lucas, A. I.; Díaz, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2917; (c) Sadashiva, B. P. S.; Nanjunda, S. S.; Mahendra, M.; Shashidhara, P. J.; Viswanath, B. S.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3679.
6. (a) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2003**, *44*, 8417; (b) Sadashiva, B. P. S.; Mantelingu, K.; Nanjunda, S. S.; Rangappa, K. S. *Bioorg. Med. Chem.* **2003**, *11*, 4539; (c) Ulgheri, F.; Bacsa, J.; Nassimbeni, L.; Spanu, P. *Tetrahedron Lett.* **2003**, *44*, 671.
7. (a) Rode, H.; Koerbe, S.; Besch, A.; Methling, K.; Loose, J.; Otto, H. H. *Bioorg. Med. Chem.* **2006**, *14*, 2789; (b) Fiorino, F.; Caliendo, G.; Perissutti, E.; Severino, B.; Frecentese, F.; Preziosi, B.; Izzo, A. A.; Capasso, R.; Santagada, V. *Arch. Pharm.* **2005**, *338*, 548; (c) Gabriel, K. I.; Cunningham, C. L. *Alcohol Clin. Exp. Res.* **2005**, *29*, 75; (d) Kuhn, C.; Bufe, B.; Winnig, M.; Hofmann, T.; Frank, O.; Behrens, M.; Lewtschenko, T.; Slack, J. P.; Ward, C. D.; Meyerhof, W. *J. Neurosci.* **2004**, *24*, 10260; (e) Lai, Z.; Gan, X.; Wie, L.; Alliston, K. R.; Yu, H.; Li, Y. H.; Groutas, W. C. *Arch. Biochem. Biophys.* **2004**, *429*, 191; (f) Araújo, N. C. P.; Barroca, P. M. M.; Bickley, J. F.; Brigas, A. F.; Cristiano, M. L. S.; Johnstone, R. A. W.; Loureiro, R. M. S.; Pen, P. C. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, *9*, 1213; (g) Caliendo, G.; Fiorino, F.; Perissutti, E.; Severino, B.; Scolaro, D.; Gessi, S.; Cattabriga, E.; Borea, P. A.; Santagada, V. *Eur. J. Pharm. Sci.* **2002**, *16*, 15.
8. (a) Xu, L.; Shu, H.; Liu, Y.; Zhang, S.; Trudell, M. L. *Tetrahedron* **2006**, *62*, 7902; (b) Rode, H. B.; Sprang, T.; Besch, A.; Loose, J.; Otto, H. H. *Pharmazie* **2005**, *60*, 723; (c) Ersanli, C. C.; Odabasoglu, M.; Sari, U. *Acta Crystallogr., Sect. C* **2005**, *61*, 243; (d) Lai, Z.; Gan, X.; Wei, L.; Alliston, K. R.; Yu, H.; Li, Y. H.; Groutas, W. C. *Arch. Biochem. Biophys.* **2004**, *429*, 191; (e) Brooke, C. G.; Davies, S. G.; Mulvaney, A. W.; Okada, M.; Pompeo, F.; Sim, E.; Vickers, R. J.; Westwood, I. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2527; (f) Elgazwy, A.-S. S. H. *Tetrahedron* **2003**, *59*, 7445; (g) Soubh, L.; Besch, A.; Otto, H. H. *Pharmazie* **2002**, *57*, 384; (h) Nerenberg, J. B.; Erb, J. M.; Thompson, W. J.; Lee, H. Y.; Guare, J. P.; Munson, P. M.; Bergman, J. M.; Huff, J. R.; Broten, T. P.; Chang, R. S.; Chen, T. B.; O'Malley, S.; Schorn, T. W.; Scott, A. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2467.

9. (a) Yu, Z.-X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 13825; (b) Lee, G. *Synthesis* **1982**, 508.
10. (a) Lyashchenko, G. S.; Medvedeva, A. S.; Safronova, L. P.; Bannikova, O. B.; Voronkov, M. G. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1991**, *12*, 2520; (b) Inoue, Y.; Taguchi, M.; Toyofuku, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3021; (c) Dahlbom, R.; Karlén, B.; George, R.; Jenckn, D. J. *J. Med. Chem.* **1966**, *9*, 843; (d) Rice, H. L.; Pettit, G. R. *J. Am. Chem. Soc.* **1954**, *76*, 302; (e) Merritt, L. L.; Levey, J. S.; Cutter, H. B. *J. Am. Chem. Soc.* **1939**, *61*, 15.
11. (a) Radhakrishna, A. S.; Sivaprakash, K.; Singh, B. B. *Synth. Commun.* **1991**, *21*, 1625; (b) Whitney, R. A.; Nicholas, E. S. *Tetrahedron Lett.* **1981**, *35*, 3371; (c) Grundmann, C. *Synthesis* **1970**, 344; (d) Grundmann, C.; Datta, S. *J. Org. Chem.* **1969**, 2016.
12. Lu, T.-J.; Tzeng, G.-M. *J. Chin. Chem. Soc.* **2000**, *47*, 189.
13. (a) Shu, C.-M.; Lin, W.-L.; Lee, G.-H.; Peng, S.-M.; Chung, W.-S.; Wu, S.-H. *J. Chin. Chem. Soc.* **2000**, *47*, 173; (b) Kurth, M. J.; Schore, N. E.; Beebe, X. *J. Org. Chem.* **1995**, *60*, 4196; (c) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8645; (d) Kurth, M. J.; Olmstead, M. M.; Rodriguez, M. J. *J. Org. Chem.* **1990**, *55*, 283; Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
14. (a) Vo-Thanh, G.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 9091; (b) Loupy, A.; Chatti, S.; Delamare, S.; Lee, D.-Y.; Chung, J.-C.; Jun, C.-H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1280.
15. (a) Bougrin, K.; Bennami, A. K.; Fkih-Tetouani, S.; Soufiaoui, M. *Tetrahedron Lett.* **1994**, *35*, 8373; (b) Reddy, A. C. S.; Rao, P. S.; Venkataratnam, R. V. *Tetrahedron Lett.* **1996**, *37*, 3845; (c) Loupy, A.; Perreux, L.; Liagre, M.; Burle, K.; Moneuse, M. *Pure Appl. Chem.* **2001**, *73*, 161.
16. (a) Vo-Thanh, G.; Lahrache, H.; Loupy, A.; Kim, I. J.; Chang, D. H.; Jun, C. H. *Tetrahedron* **2004**, *60*, 5539; (b) Loupy, A.; Maurel, F.; Sabatié-Gogova, A. *Tetrahedron* **2004**, *60*, 1683.
17. Perreux, L.; Loupy, A. In *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006; Chapter 4.