Thermochimica Acta 501 (2010) 30–34

Contents lists available at ScienceDirect

Thermochimica Acta

journal homepage: www.elsevier.com/locate/tca

Alternative synthetic strategies for new drug candidates. The thermolysis reaction of N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide to yield benzylsulfamide

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ARTICLE INFO

Article history:
Received 13 October 2009
Received in revised form
21 December 2009
Accepted 22 December 2009
Available online 11 January 2010

Keywords:
Thermolysis reaction
Sulfamides

ABSTRACT

The hydrolysis of one sulfamide derivative under conventional conditions and under thermolysis reaction has been investigated. Comparison between these techniques revealed advantages in the use of thermal decomposition reaction to obtain sulfamides, due to the easy elimination of gaseous by-products produced in the reaction.

1. Introduction

Sulfamides represent an interesting target in the field of medicinal chemistry. The sulfamide functional group comes out as one of the most relevant structural motifs found in high affinity protein ligands and pharmaceutically useful agents. Compounds bearing this functionality have been tested as HIV protease inhibitors [1,2], agonists of the 5-HTID receptor [3], active components in epinephrine analogues [4], non-hydrolizable components of peptide-mimetics [5] and carbonic anhydrase inhibitors [6–10]. Additionally, previous research from some of us and other authors has considered alkyl/aryl sulfamides as new candidates for antiepileptic drugs: Structures with the sulfamide function were found active against one of the most widely used experimental models for the preclinical stage in epilepsy research (MES test) [11,12].

The selection of the synthetic routes to obtain sulfamides is related to the position of the substituents. Symmetric N,N′-disubtituted and tetrasubstituted sulfamides were prepared by condensation of an excess of amine with sulfuryl chloride [13–17]. In case of mono-substituted and N,N-disubstituted compounds, the standard reaction involves the preparation of the N-alkoxycarbonyl sulfamide derivative (compound named II, Scheme 1) followed by acidic hydrolysis [18–22]. This intermediate was prepared from chlorosulfonyl isocyanate, *tert*-butanol, and the corresponding amine in presence of triethylamine (TEA). The *tert*-butoxycarbonyl group was then removed via trifluoroacetic acid (TFA) [8,18–21].

Efficient synthetic procedures become relevant for rational drug design methodologies. The promising results obtained in the biological stages for sulfamides and their derivatives, encourage us to develop new synthetic strategies, in order to reduce the generation of waste, and to avoid the use of toxic (and/or hazardous) reagents and solvents.

Previous efforts to improve the synthetic method outlined in Scheme 1 were performed by other investigators [23–24]. The first step in the reaction involves the synthesis of N-(*tert*-butoxycarbonyl)aminosulfonyl chloride (compound I, Scheme 1), a very instable intermediate against moisture. The generation of the corresponding Burgess-type salt deactivates the intermediate I and allows the subsequent reaction in mild conditions [23]. An alternative method was also proposed for the removal the carbamate group of II, using a microwave-assisted method with silica-phenyl sulfonic acid [24]. Following this line, we have focused this investigation on the improvement of the last step of the reaction showed in Scheme 1 by means of the substitution of the hydrolysis reaction by the thermal decomposition of II, to obtain mono-substituted and N,N-disubstituted sulfamides. This alternative method results beneficial in several aspects, since the abolition of other reactants and solvents reduce the impact on human health and the environment. Furthermore, it is expected an improvement in the yield of the thermolysis reaction, because the work up for the recovery of the desired compound from the conventional reaction systems always results in some losses.

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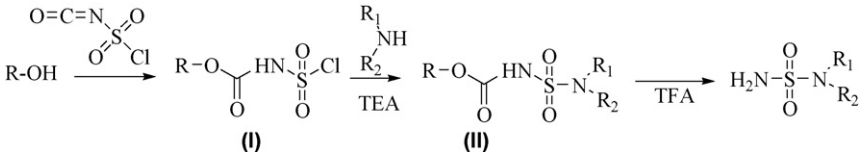
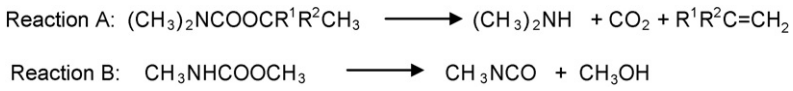
doi:10.1016/j.tca.2009.12.019



Scheme 1. Synthetic route for mono-substituted and N,N-disubstituted sulfamides [18–22]. R = *tert*-butyl; R1, R2 = alkyl, aryl, H.



Scheme 2. Thermolysis reaction of N,N-dialkyl carbamates (reaction A) and mono-subsituted carbamates (reaction B).

We are not aware of any publication related to the study of the mechanism of the thermolysis of N-alkoxycarbonyl sulfamides, so we considered as reference the thermal decomposition of carbamates in the gas phase. The generally accepted mechanism of decomposition of N,N-dialkyl carbamates implies an elimination process, through a six-membered cyclic transition state to give the corresponding amine, the alkene and CO_2 (reaction A, Scheme 2) [22,25–27]. In mono-substituted carbamates, the presence of a hydrogen atom attached to the nitrogen atom is believed to be responsible for the different mechanistic pathway, and the elimination reaction proceeds via a four member cyclic transition state, to give the corresponding isocyanate and the alcohol molecules (reaction B, Scheme 2) [27].

The investigation presented herein analyzes, as a test example, the thermolysis reaction of N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide (structure II, Scheme 3). If the thermal decomposition takes place in a similar pathway than carbamates (pathway A, Scheme 2), the reaction would yield the expected sulfamide (structure III, Scheme 3) and gaseous sub products that can be easily eliminated of the reaction bulk. Accordingly, we have compared and characterized the sulfamide obtained from the standard hydrolysis of II with the product that results from its thermal decomposition reaction. To the characterization we have used Infrared spectroscopy, thin-layer chromatography and nuclear magnetic resonance spectroscopy. Additionally, the gaseous by-products of the thermolysis reaction were analyzed via GC-TCD/MS.

2. Experimental procedure

2.1. Synthesis of N-(benzyl)-N′-(tert-butoxycarbonyl) sulfamide (II)

This compound was prepared according to the general procedure detailed in literature, using a solution of chlorosulfonyl isocianate in CH_2Cl_2, *tert*-butanol, benzylamine and triethylamine (firt step in Scheme 1, R = *tert*-butyl, R1 = benzyl, R2 = H) [12].

2.2. Synthesis of benzylsulfamide (III)

As explained before, the standard hydrolysis method involves the acidic hydrolysis with a solution of TFA in dried CH_2Cl_2, until disappearance of the sulfonyl carbamate II [12]. Then, the reaction mixture is concentrated, and the excess of TFA is co-evaporated with diethyl ether [12].

The products II and III were characterized and identified using thin-layer chromatography, IR spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy and elemental analysis [12].

2.3. Thermal stability of N-(benzyl)-N′-(tert-butoxycarbonyl)sulfamide and benzylsulfamide

In order to study the thermal stability of the structures, gravimetric thermal analysis (TGA) were performed for compounds II and III, with a Shimadzu TGA 50 apparatus. 5 mg of compounds were loaded in an aluminum crucible and heated from room temperature (5 °C/min) in helium flow (20 mL/min) to 200 °C.

2.4. Thermolysis test

The thermolysis tests were performed by gravimetric thermal analysis (TGA) with a Shimadzu TGA 50 apparatus. 5 mg of compound II were loaded in an aluminum crucible and heated from room temperature (5 °C/min) in helium flow (20 mL/min) to 115 °C.

2.5. Characterization of the product obtained by thermolysis

2.5.1. Infrared spectroscopy (IR)

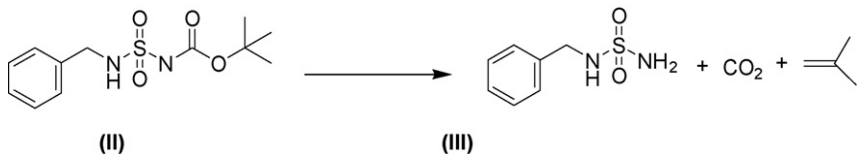
The FTIR spectra were carried out with an EQUINOX 55 spectrophotometer, from 4000 to 400 cm^{-1} and the samples were prepared in form of pills with KBr. Only significant absorption bands were reported here.

2.5.2. Thin-layer chromatography (TLC)

The chromatographic procedures were performed with aluminum backed sheets with silica gel 60 F254 (Merck, ref 1.05554), and the mixture CH_2Cl_2:MeOH 30:1 was used as the elution solvent. The spots were visualized with UV light (254 nm) and 5% aqueous solution of ammonium molybdate (VI) tetrahydrate. The results were expressed as retention factor values (Rf).

2.5.3. Nuclear magnetic resonance spectroscopy (NMR)

Two hundred megahertz ^{1}H NMR and 75.4 MHz ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer. The chemical



Scheme 3. Thermolysis reaction proposed for N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide.

shifts are reported in ppm (δ scale) relative to internal tetramethylsilane (TMS), and coupling constants are reported in Hertz (Hz). We have used chloroform ($CDCl_3$) solvent for compound II, and dimethyl sulfoxide (DMSOd6) for the sulfamide obtained by traditional synthesis III and for the product of thermal decomposition.

2.6. GC–mass spectroscopy

The secondary gaseous products of the reaction were analyzed using a gas chromatograph (Shimadzu 8-A) with a TCD detector on line with a fixed bed reactor, which was fed with helium and heated electrically from 30 °C up to 115 °C (and kept for 3 h at this temperature). This technique allowed us the quantitative determination of CO_2 generated as by-product in the reaction.

Additionally, a mass spectrometer (Dycor System 2000) was incorporated to the apparatus, on line with the reactor, in order to detect all gaseous by-products.

3. Results and discussion

3.1. Stability assays of compounds II and III

Heat stability assays were performed for 5 mg of compound II, using a thermal gravimetric analyzer. The same experience was carried out for 5 mg of compound III. The resulting TGA diagrams are given in Fig. 1.

Fig. 1 indicates the thermal decomposition of the product and the reactive. The benzylsulfamide decomposition starts at 140 °C, and the N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide decompose at 100 °C. If we assumed that the thermolisys of compound II generates benzylsulfamide III, carbon dioxide and gaseous hydrocarbon sub products, the theoretical relative loss of mass would be 35.6%. According to the TGA results, the loss in mass of compound II was calculated as 34.0% relative to the initial sample, which corresponds to a high degree of conversion, near to 95.5%.

Consistent with the TGA experiences, an intermediate temperature between 100 and 140 °C was selected to obtain the compound III in isothermal conditions. Fig. 2 shows the weight loss of II to obtain III at 115 °C.

The weight loss curve observed for compound II at 115 °C (Fig. 2) pointed out a decrement in the mass that starts at the beginning of the reaction and ends with a constant mass value after 110 minutes of heating. In this isothermal experience the relative loss of mass was 31%, with a yield of 87.1%. The achievement of the product with a higher degree of conversion and a shorter reaction time relative to the traditional hydrolysis (yield: 62%, 14 h) [12] represents an important optimization for this synthetic step.

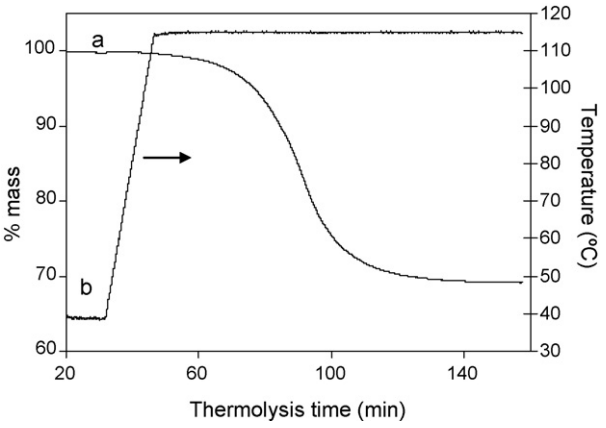


Fig. 2. TGA diagrams that characterize the synthesis of benzylsulfamide by thermolysis. (a) Weight loss of II relative to the initial sample and (b) temperature.

3.2. Characterization of the products obtained by thermolysis

Table 1 shows the retention factors (Rf) found in TLC for compounds II, III and for the product obtained by thermolysis. In the last case, TLC showed two spots with Rf values that match with the corresponding ones for compounds II and III. This fact probably indicates that the desired product was obtained by heating, but the reaction was incomplete. This observation is consistent with the results found in TGA, where we assumed an incomplete reaction due to the weight loss observed.

Another qualitative analysis of the samples was performed by vibrational spectroscopy. Fig. 3 shows the FTIR spectra recorded for compound III and for the product obtained by thermolisys. Both spectra are similar, and they present absorption bands that are characteristic for the expected functional groups SO_2, NH and NH_2. In case of the sample obtained from thermolysis, there is a small band associated with the presence of carbonyl group (1680 cm^{-1}), showing again an incomplete transformation of the reactant II. The most significant absorption bands are summarized in Table 1.

To facilitate a more reliable detection of the product obtained from thermolysis, the sample was purified following crystallization standard procedures [12]. The pure solid obtained (white crystals,

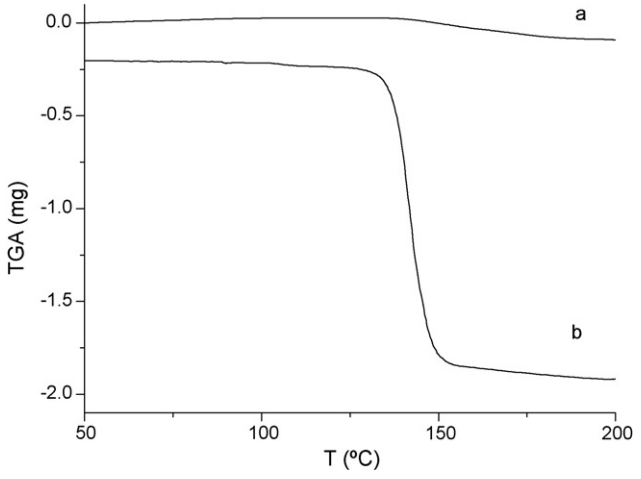


Fig. 1. TGA diagrams that illustrate the weight loss of: (a) benzylsulfamide III and (b) N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide II. Mass: 5 mg, QHe = 20 mL/min, heat rate: 5 °C/min.

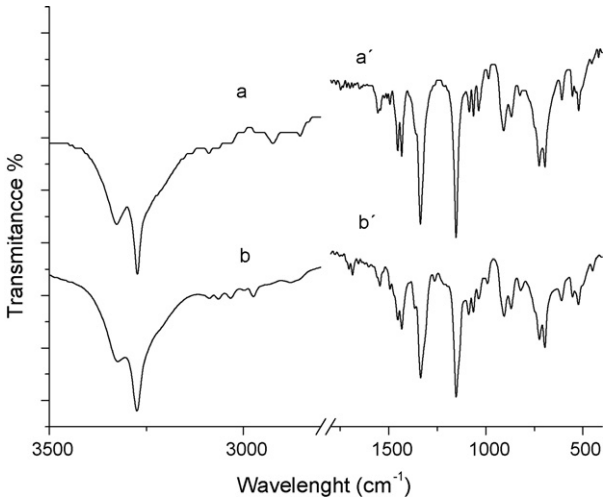


Fig. 3. FTIR spectra of: (a and a′) benzylsulfamide; (b and b′) N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide treated at 115 °C in helium flow.

Table 1
Characterization of N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide, and benzylsulfamide obtained by hydrolysis and thermolysis.

Compound	IR[a]	TLC	NMR[b]	
			^{1}H NMR	^{13}C NMR
N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide	3300, 3273 (NH), 3068, 3033 (CH, Ar), 1713 (C=O), 1358, 1148 (SO_2)	Rf: 0.62	7.35–7.26 (m, 6H: Ar–H and NH-Boc), 5.61 (t, broad signal, $J \approx 6.1$ 1H: NH-Bz), 4.25 (d, $J = 6.1$, 2H: CH_2), 1.44 (s, 9H: CH_3 *tert*-Bu)	150.37 (C=O), 135.88 (C^1–Ar), 129.09, 128.36, 128.33 ($C^{2,3,4}$–Ar), 84.09 ($C(CH_3)_3$), 45.81 (CH_2), 28.20 (CH_3, *tert*-Bu)
Benzylsulfamide	3325, 3273 (NH, NH_2), 3039 (CH, Ar), 1334, 1153 (SO_2)	Rf: 0.30	7.41–7.19 (m, 5H: Ar–H), 7.00 (t, $J = 6.6$ Hz, 1H: NH-benzyl), 6.59 (s, 2H: NH_2), 4.05 (d, $J = 6.6$, 2H: CH_2)	139.36 (C^1–Ar), 127.61, 128.35, 128.85 ($C^{2,3,4}$–Ar), 46.79 (CH_2)
N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide treated at 120 °C in Helium flow	3325, 3273 (NH, NH_2), 3039 (CH, Ar), 1334, 1153 (SO_2). Residual peak of C=O (1681)	Rf1: 0.30; Rf2: 0.60	7.33–7.24 (m, 5H: Ar–H), 7.01 (t, $J = 6.3$ Hz, 1H: NH-benzyl), 6.60 (s, 2H: NH_2), 4.05 (d, $J = 6.3$, 2H: CH_2)	139.32 (C^1–Ar), 127.55, 128.32, 128.81 ($C^{2,3,4}$–Ar), 46.74 (CH_2)

[a] IR absorption values are expressed as wave numbers (cm^{-1}); only significant absorption bands are given.
[b] The NMR chemical shifts are reported in ppm (δ scale) relative to internal TMS, and coupling constants are reported in Hertz (Hz).

Fig. 4. Production of gaseous CO_2 in the reactor, identified with a TCD detector.

Rf = 0.30) was analyzed using nuclear magnetic resonance spectroscopy (NMR). The chemical shift found for the purified product match completely with the corresponding signals obtained from compound III (Table 1). Additionally, there are no extra signals associated with the carbamate group, which is present in the structure of the reactant II.

The secondary products of the reaction were analyzed using a fixed bed reactor, which was fed with helium and set on line to a gas chromatograph with a TCD detector. Additionally, a mass detector was incorporated to the apparatus, in order to get more information about the gaseous by-products. According to the GC-TCD analysis, gaseous CO_2 was produced after heating compound II in the reactor at 115 °C (Fig. 4). The calculated yield relative to the CO_2 production is 78.3%.

The mass detector corroborated the presence of CO_2 ($m/z = 44$), and detected another characteristic peaks for 2-methylpropene ($m/z = 56$ and 41). This alkene was expected to be obtained if the thermal decomposition of III proceeds in a similar pathway than the carbamates previously studied (Scheme 3) [25–27]. It is worth mentioning that no charged fragments from isopropanol or isocianate group were detected from mass spectroscopy.

4. Conclusions

The experimental data presented herein allowed us to characterize and identify the products obtained by thermolysis of N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide. By comparison of the result obtained from TLC, IR and RMN spectroscopy, we can conclude that the controlled heating of N-(benzyl)-N′-(*tert*-butoxycarbonyl)sulfamide yields benzylsulfamide in a clean and efficient manner.

The analysis of gaseous by-products encourage us to suggest that the decomposition proceeds in a similar route than N,N-dialkyl carbamates (reaction A, Scheme 2), giving CO_2 and 2-methylpropene as secondary products. These molecules can be easily eliminated from the reaction bulk, making easier the workup procedure to obtain the pure benzylsulfamide. Additionally, the thermolysis reaction proceeds faster than traditional hydrolysis and it is not assisted by other reactants and solvents. The consideration of these experimental advantages allowed us to determine that the thermolysis reaction is a suitable synthetic alternative for the preparation of this kind of compounds.

Acknowledgements

L.E. Bruno-Blanch is a member of the Facultad de Ciencias Exactas, Universidad Nacional de La Plata; E.N. Ponzi, I.D. Lick and

L. Gavernet are researchers from Consejo Nacional de Investigaciones Cientiíficas y Tecnicas de la Republica Argentina (CONICET). This research was supported in part through grants from Agencia de Promoción Científica y Tecnológica, CONICET, and Universidad Nacional de La Plata, Argentina.

References

[1] K. Bäckbro, S. Lowgren, K. Osterlund, J. Atepo, T. Unge, J. Hulten, N.M. Bonham, W. Schaal, A. Hallberg, J. Med. Chem. 40 (1997) 898–902.
[2] J. Hulten, N.M. Bonham, U. Nillroth, T. Hansson, G. Zuccarello, A. Bouzide, J. Aqvist, B. Classon, U.H. Danielson, A. Karlen, I. Kvarnstrom, B. Samuelsson, A. Hallberg, J. Med. Chem. 40 (1997) 885–897.
[3] J.L. Castro, R. Baker, A.R. Giublin, S.C. Hobbs, M.R. Jenkins, M.G. Rusell, M.S. Beer, J.A. Stanton, K. Scholey, R.J. Hargreaves, J. Med. Chem. 37 (1994) 3023–3032.
[4] R.M. Acheson, M.G. Bite, J.E. Kemp, J. Med. Chem. 24 (1981) 1300–1304.
[5] J.M. Dougherty, D.A. Probs, R.E. Robinson, J.D. Moore, T.A. Klein, K.A. Snelgrove, P.R. Hanson, Tetrahedron 56 (2000) 9781–9790.
[6] F. Abbate, C.T. Supuran, A. Scozzafava, P. Orioli, M.T. Stubbs, G. Klebe, J. Med. Chem. 45 (2002) 3583–13583.
[7] J.Y. Winum, A. Innocenti, J. Nasr, J.L. Montero, A. Scozzafava, D. Vullo, C.T. Supuran, Bioorg. Med. Chem. Lett. 15 (2005) 2353–2358.
[8] A. Casini, J.L. Winum, J.L. Montero, A. Scozzafava, C.T. Supuran, Bioorg. Med. Chem. Lett. 13 (2003) 837–840.
[9] J.Y. Winum, A. Cecchi, J.L. Montero, A. Innocenti, A. Scozzafava, C.T. Supuran, Bioorg. Med. Chem. Lett. 15 (2005) 3302–3306.
[10] B.E. Maryanoff, D.F. McComsey, M.J. Costanzo, C. Hochman, V. Smith-Swintosky, R.P. Shank, J. Med. Chem. 48 (2005) 1941–1947.
[11] L. Gavernet, J. Dominguez Cabrera, L.E. Bruno-Blanch, G.L. Estiú, Bioorg. Med. Chem. 15 (2007) 1556–1567.
[12] L. Gavernet, I. Barrios, M. Sella Cravero, L.E. Bruno-Blanch, Bioorg. Med. Chem. 15 (2007) 5604–5614.
[13] M. Bermann, J.R. Van Wazer, Synthesis 10 (1972) 576–577.
[14] B. Gong, C. Zheng, E. Skrzpczak-Jankun, Y. Yan, J. Zhang, J. Am. Chem. Soc. 120 (1998) 11194–11195.
[15] B. Gong, C. Zheng, E. Skrzpczak-Jankun, Y. Yan, J. Zhang, J. Am. Chem. Soc. 121 (1999) 9766–9767.
[16] A. Vandi, T. Moeller, L.F. Audrieth, J. Org. Chem. 26 (1961) 1136–1138.
[17] V.R. Sowada, J. Prakt. Chem. 20 (1963) 310–319.
[18] G.F. Dewynter, J.L. Montero, R. Acad. Sci. Paris Ser. II 315 (1992) 1675–1682.
[19] J.A. Picard, P.M. O'Brien, D.R. Sliskovic, M.K. Anderson, R.F. Bousley, K.L. Hamelehle, B.R. Krause, R.L. Stanfield, J. Med. Chem. 39 (1996) 1243–1252.
[20] J.Y. Winum, L. Toupet, V. Barragan, G. Dewynter, J.L. Montero, Org. Lett. 3 (2001) 2241–2243.
[21] M. Abdaoui, G. Dewynter, N. Aouf, G. Favre, A. Morere, J.L. Montero, Bioorg. Med. Chem. 4 (1996) 1227–1235.
[22] N.J. Daly, F. Ziolkowski, Aust. J. Chem. 24 (1971) 2451–2544.
[23] T. Masui, M. Kabaki, H. Watanabe, T. Kobayashi, Y. Masui, Org. Process. Res. Dev. 8 (2004) 408–410.
[24] G. Shahnaz, K. Fuchs, Mol. Diver. 9 (2005) 295–299.
[25] C. Marcano, M. Loroño, T. Cordova, G.I. Chuchani, J. Mol. Struct.: THEOCHEM 764 (2006) 201–204.
[26] C. Quijano, R. Notario, J. Quijano, C. Sanchez, L.A. Leon, E. Velez, Theor. Chem. Acc. 110 (2003) 377–386.
[27] N.J. Daly, F. Ziolkowski, Aust. J. Chem. 25 (1972) 1453–1458.