A Practical and Eco-Friendly Synthesis of Stereocontrolled Alkylaminomethylidene Derivatives of 2-Thiohydantoins by Dimethylamine Substitution.

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A practical and eco-friendly synthesis of stereocontrolled alkylaminomethylidene derivatives of 2-thiohydantoins by dimethylamine substitution

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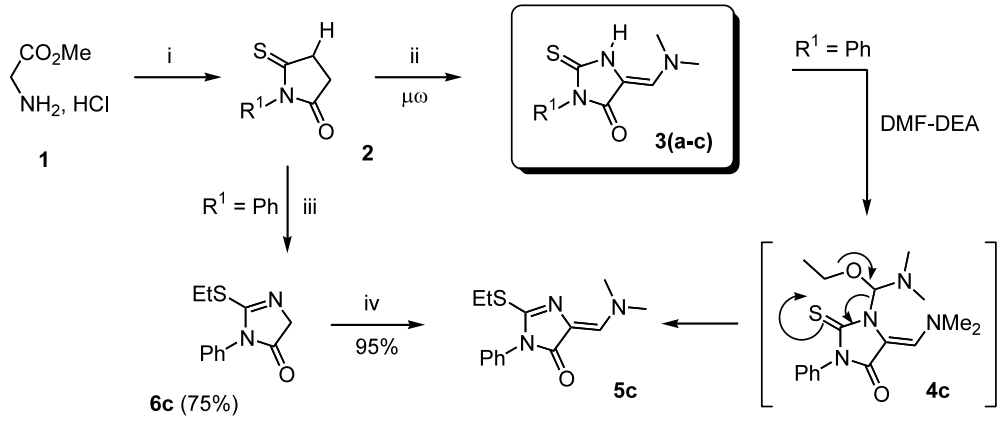
Abstract—3-Alkyl-5-dimethyaminomethylidene-2-thioxo-imidazolidin-4-ones **3(a–c)** available in two steps from methyl glycinate hydrochloride, represent a useful synthetic tool for efficient and mild solventless preparations of new alkylaminomethylidene derivatives of 2-thiohydantoins **8(a–e)**, **10(a–c)** and **12(a–d)** by stereocontrolled transamination reactions under microwave irradiations. The ^{1}H, ^{13}C NMR spectrum and the (5*Z*)-conformation of some representatives products are also discussed.

Derivatives of 2-thiohydantoins play an important role in organic synthesis, especially as starting materials for the preparation of synthetic intermediates with a wide range of applications as therapeutics[1] as well as fungicides and herbicides.[2] Among these compounds the S-glucosylated hydantoins[3] exhibit properties against the herpes simplex virus[4] (HSV), the human immunodeficiency virus[5] (HIV). Recently, a series of S-alkylated 4-ylidene thiohydantoins have been prepared in our laboratory as versatile reagents for the synthesis of marine alkaloid 2-amino imidazolones[6] derivatives for investigations of protein kinase C inhibition activities,[7] using solventless Knoevenagel reaction conditions under microwave irradiations.

Owing to economic and ecological reasons, organic synthetic chemists in pharmaceutical industry face an



Scheme 1. *Reagents and conditions:* (i) TEA 1 equiv., R^1NCS 1 equiv., Et_2O or AcOEt, reflux, 15 h; (ii) DMF–DEA 1.05 equiv., μω (in the Synthewave® 402 reactor), for **3a**: R^1 = Me, 70°C, 15–30 min (74%), for **3b**: R^1 = Bu, 80°C, 45 min (77%), for **3c**: Ph, 70°C, 30 min (75%); (iii) K_2CO_3 0.55 equiv., EtI 1.1 equiv., 65°C, MeCN, 14 h; (iv) DMF-DEA 1 equiv., 70°C, 1 h.

Keywords: transamination reactions; dimethylamine substitutions; microwaves; thiohydantoins; alkylaminomethylidene-2-thioxo-imidazolidin-4-ones.

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increasing obligation to optimize the quantities of volatile organic solvents (VOCs) and toxic waste in chemical processes.[8] Thus, the development of solvent-free organic synthesis under microwaves has received much attention.[9]

In the course of identifying new chemical structures derived from 2-thiohydantoins for their biological activities,[10] we were interested to develop a new route to alkylamino derivatives of 2-thiohydantoins towards new, simple and efficient procedures.

Scheme 1 shows the route for the preparation of 3-alkyl-5-dimethylaminomethylene-2-thioxo-imidazolidin-4-ones **3(a–c)**. In the first step, the 3-substituted-2-thioxo-imidazolidin-4-ones **2(a–c)** (R^1 = Me, Bu, Ph) were readily available in large scale (up to 20 g) with good yields (~96%) by addition of commercial isothiocyanates to methyl glycinate hydrochloride in basic medium.[6] For the second step, we have investigated the reactivities of 2-thioxo-imidazolidin-4-ones derivatives **2(a–c)** with *N*,*N*-dimethylformamide diethylacetal[11] (DMF–DEA) using solvent-free conditions under microwave irradiations. The microwave instrument (Synthewave® 402 reactor[12]) comprises a monomode (sometimes also called single-mode) microwave cavity that operates at a frequency of 2.45 GHz with continuous microwave irradiation power from 0 to 300 W.

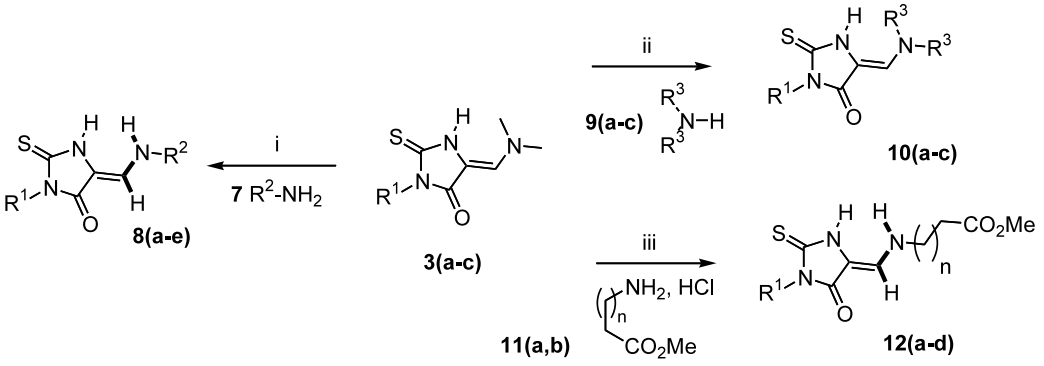
The reaction vial is a cylindrical quartz reactor (Ø = 4 cm) which was introduced into the Synthewave® 402 microwave reactor. Inside the microwave cavity the vial was exposed to microwave irradiations. The temperature was measured with an IR captor[13] (infrared thermometry). The software algorithm regulates the microwave output power so that the preselected maximum temperature is maintained for the desired reaction/irradiation time. After the irradiation period, the reaction vial is cooled rapidly to ambient temperature by compressed air (gas jet cooling).

The 2-thioxo-imidazolidin-4-ones **2(a–c)** were converted with DMF-DEA (1.05 equiv.) into the corresponding 5-dimethylaminomethylidene-2-thioxo-imidazolidin-4-ones **3(a–c)** in yields ranging from 74 to 77% after a reaction time of ~30 minutes at 70–80°C under microwave irradiations.[14] From **2c** (R^1 = Ph) we have also observed that ethylation at the exocyclic sulfur[15] took place to give 5-dimethylaminomethylidene-3-phenyl-2-ethylsulfanyl-3*H*-imidazol-4(5*H*)-one **5c** in ~10% yield via the intermediate **4c** which could not be isolated (Scheme 1). The structure of **5c** was confirmed by S-alkylation[16] (with ethyliodide) of **2c** (R^1 = Ph) in basic medium (K_2CO_3 0.55 equiv.) which provided 2-ethylsulfanyl-3-phenyl-3,5-dihydro imidazol-4-one **6c** in 75% yield, then **6c** was transformed with DMF–DEA (1 equiv.) at 70°C into **5c** in 95% yield after 1 hour. The expected compounds **3(a–c)**, **5c** and **6c** were purified by recrystallization.

The 5-dimethylaminomethylidene-3-substituted-2-thioxo-imidazolidin-4-ones **3(a–c)** and compound **5c** can exist in (5*Z*) and/or (5*E*) isomeric forms with respect to the exocyclic C=C double bond. In all cases, the compounds **3(a–c)** exist as single isomers, as shown by the presence of only one set of signals in each of ^{1}H and ^{13}C NMR, but differentiation between (*Z*)- and (*E*)-form is not possible on the basis of chemical shifts. However, the two isomeric forms are easily differentiated on the basis of the magnitude of the long range heteronuclear ^{13}C–^{1}H coupling constants, $^3J_{CH}$ which have been used for determination of configuration in various systems.[17] Generally, the magnitude of coupling constant for *cis*-configuration around the C=C double bond is smaller (2–6 Hz) than for *trans*-oriented nuclei (8–12 Hz). In the case of compound **3a**[18] (R^1 = Me), the magnitude of coupling constant $^3J_{CH}$ = 3.4 Hz showed that **3a** exist in the (Z) form.

With compounds **3(a–c)** in hand, we then studied their reactivity in transamination reactions[19] with various primary aliphatic amines **7(a–c)** using solvent-free technique under microwave irradiations[20] (Scheme 2). Several experiments were performed with **3a** (R^1 = Me), at various powers and irradiations times, with an excess of amine **7** (2–10 equiv.) in order to find the most adequate reaction conditions under microwave. The optimized reaction conditions were summarized in Table 1.

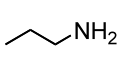
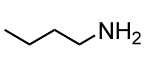
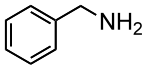
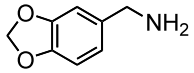
The expected compounds **8(a–e)** were isolated from the crude reaction mixture (after elimination of the excess

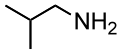
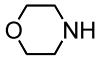


Scheme 2. *Reagents and conditions*: (i) **7** 2–10 equiv., μω (in the Synthewave® 402 reactor), 15–30 min, 50–70°C; (ii) **9** 5 equiv., μω, 80°C, 30 min; (iii) **11** 1 equiv., $MeCO_2H$, μω, 95°C, 90 min.

Table 1. 5-Alkylaminomethylidene-3-methyl-2-thioxo-imidazolidin-4-ones **8(a–e)** and **10(a–c)** prepared by transamination reactions from **3a** ($R^1 = Me$), primary amines **7(a–e)** and cycloalkylamines **9(a–c)**

Amine **7** or **9**	Ratio **3a**/amine **7** or **9**	Product **8** or **10**	Reaction conditions[a]		Yield of **8** or **10** (%)[b]
			Reaction time (min)	Temperature (°C)	
7a	1:10	**8a**	15	50	88
7b	1:10	**8b**	60+30	70	68
7c	1:4	**8c**	30	70	67
7d	1:2	**8d**	30	70	56
7e	1:5	**8e**	30	60	58
9a	1:5	**10a**	30	80	63
9b	1:5	**10b**	30	80	53
9c	1:5	**10c**	30	80	72

7a :  **7b :**  **7c :**  **7d :** 

7e :  **9a :**  **9b :**  **9c :** 

[a] The reactions were performed under microwave irradiation in the Synthewave® 402 reactor.
[b] Isolated yield of **8** or **10**.

of amine **7** and dimethylamine in vacuo) by crystallization and repeated washings with ether or pentane in yields ranging from 56 to 88% (Table 1). The structure of the new 5-alkylaminomethylidene-2-thioxo-imidazolidin-4-ones **8(a-e)** were substantiated by the ^1H, ^{13}C and HRMS analyses.

A characteristic feature of the ^1H NMR spectra of 5-alkylaminomethylidene-3-methyl-2-thioxo-imidazolidin-4-ones **8(a–e)** is the downfield shift of the doublet for the exocyclic C=CH double bond (**8a**: $\delta_{vinyl} = 6.93$ ppm). The coupling constant $^3J = 13.2$ Hz between the aminoproton NH and exocyclic vinyl proton CH suggests the *trans* (antiperiplanar) orientation[21] of these hydrogens. Futhermore, the shift of H-1 (NH) has been found at low field (**8a:** $\delta_{H\text{-}1} = 11.1$ ppm). The shift of the CH signal for the exocyclic double bound C=CH is confirmed in the ^1H resonance-coupled ^{13}C NMR spectra by identification of a doublet centered at $\delta_{CH} =$ 130.80 ppm for **8a**[22] ($J = 173$ Hz).

In order to define the ability of the 5-dimethylaminomethylidene-2-thioxo-imidazolidin-4-ones **3** for transamination reaction, we have also evaluated the reactivity of **3a** ($R^1 = Me$) with secondary amines **9(a–c)** using the same reaction conditions (Scheme 2). For this study, the cyclic secondary amines employed were, i.e. pyrrolidine **9a**, piperidine **9b** and morpholine **9c**. The results obtained and the isolated yields of the new 5-cycloalkylaminomethylidene-3-methyl-2-thioxo-imidazolidin-4-ones **10(a–c)** are given in Table 1. The expected compounds **10(a–c)** were produced in yields ranging from 53 to 72% and required a reaction time of 30 minutes at 80°C under microwave irradiations.

During the course of our work, we have also found that the dimethylamino group in compounds **3(a,b)** can formally be substituted with N-nucleophiles derived from aminoester hydrochlorides[23] **11(a,b)**. The following N-nucleophiles used were methyl glycinate hydrochloride **11a** ($n = 0$), and methyl 4-aminobutanoate hydrochloride **11b** ($n = 2$). They were treated with an equimolar amount of **3** in glacial acetic acid at 95°C under microwave irradiations. After heating for 90 minutes, derivatives of methyl 4-[(1-alkyl-5-oxo-2-thioxo-imidazolidin-4-ylidenemethyl)amino]acetate **12(a,b)**[24] and methyl 4-[(1-alkyl-5-oxo-2-thioxo-imidazolidin-4-ylidenemethyl)amino]butanoate **12(c,d)** were isolated in moderate yield (14–47%) (Table 2).

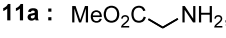
In summary, the major significance of these results is the development of a straighforward access to 5-yliden-3-alkyl-2-thioxo-imidazolidin-4-ones[25] using the eco-friendly solventless methodology assisted by microwave[26] heating. From the 2-thiohydantoins **3(a–c)**, the transamination reactions gave good results with N-nucleophiles derived from non-sterically hindered primary amines **7(a–c)**, cyclic secondary amines **9(a–c)** and moderate yields with aminoesters **11(a,b)**. Work is now in progress to study the biological potentialities[27] of these new 5-alkylaminomethylidene-3-alkyl-2-thioxo-imidazolidin-4-ones.

Acknowledgements

One of us (J.R.C.) wishes to thank the 'Conseil Régional de Bretagne' for a research fellowship (contrat N°99CBQ-4). We also thank Professor Jack Hamelin for fruitful discussions.

Table 2. Preparation of methyl 4-[(1-alkyl-5-oxo-2-thioxo-imidazolidin-4-ylidenemethyl)-amino]acetate **12(a,b)** and butanoate **12(c,d)** from **3(a,b)** and aminoesters **11(a,b)**

Aminoester **11**	*n*	Product **12**	R^1	Reaction conditions[a]		Yield of **12** (%)[b]
				Time (h)	Temp. (°C)	
11a	0	**12a**	Me	1.5	95	16
11a	0	**12b**	Bu	1.5	95	47
11b	2	**12c**	Me	1.5	95	40
11b	2	**12d**	Bu	1.5	95	30

11a : **11b :** 

[a] The reactions were performed under microwave irradiations in the Synthewave® 402 reactor.
[b] Isolated yield.

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18. Selected spectral data of *5-dimethylaminomethylidene-3-methyl-2-thioxo-imidazolidin-4-one* ***(3a)***: ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 3.09 (s, 3H), 3.11 (s, 3H), 6.79 (s, 1H, CH=), 11.10 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, TMS) δ 26.90 (q, J=141 Hz), 42.40 (q, J=158 Hz), 102.00 (d, J=7 Hz, C-5), 132.60 (dt, J=170, 3.4 Hz, C̲H=), 163.50 (dd, J=3.7, 2.4 Hz, C-4, C=O), 169.90 (q, J=3.7 Hz, C-2, C=S). HRMS, m/z=185.0623 found (calculated for $C_7H_{11}N_3OS$ requires 185.0684). mp=245–246°C.
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22. Selected spectral data of *3-methyl-5-propylaminomethyl-idene-2-thioxo-imidazolidin-4-one* ***(8a)***: ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 0.86 (t, 3H, J=7 Hz), 1.48 (q, 2H, J=7 Hz), 3.06 (s, 3H), 3.24 (d, 2H, J=4.9 Hz), 6.93 (d, 1H, J=13.2 Hz, CH=), 6.97 (br d, J=13.2 Hz, NH), 11.1 (br s, 1H, H-1). ^{13}C NMR (75 MHz, DMSO-d_6, TMS) δ 10.70 (qt, J=125, 8.4 Hz), 23.60 (tm, J=127 Hz), 26.60 (q, J=141 Hz), 49.60 (tm, J=137 Hz), 103.30 (m, C-5), 130.80 (dm, J=173 Hz, C̲H), 162.10 (m, C-4, C=O), 168.60 (d, J=8.4 Hz, C-2, C=S). HRMS, m/z=199.0782 found (calculated for $C_8H_{13}N_3OS$ requires 199.0779). mp>260°C.
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24. Preparation of *methyl 4-[(1-methyl-5-oxo-2-thioxo-imidazolidin-4-ylidenemethyl)-amino]acetate* ***(12a)***: In the Synthewave® 402 microwave reactor (Ø = 4 cm), an equimolar mixture of **3a** (1 g, 5.4 mmol.) and methyl glycinate hydrochloride **11a** (0.68 g, 5.54 mmol.) in glacial acetic acid (2 ml) was heated at 95°C under nitrogen with vigorous magnetic stirring during 1 hour under microwave irradiations. Then, the reaction mixture was allowed to cool down. After addition of MeOH (10 ml), the unsoluble compound **12a** was filtered off, washed twice with Et_2O (10 ml) and dried in a dessicator over $CaCl_2$ which gave **12a** in 16% yield as white needles (mp>260°C). ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 3.07 (s, 3H), 3.67 (s, 3H), 4.22 (d, 2H, J = 5.7 Hz), 6.90 (d, 1H, J = 13.3 Hz, CH=), 7.08-7.14 (m, 1H, NH), 11.33 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, TMS) δ 26.60 (q, J = 141 Hz), 48.4 (t, J = 141 Hz), 51.90 (q, J = 147 Hz), 104.40 (d, J = 5 Hz, C-5), 130.10 (dm, J = 175 Hz, CH), 162.50 (m, C-4), 169.70 (m, C=O), 170.50 (m, C-2, C=S). HRMS, m/z = 226.6524 found (calculated for $C_8H_{11}N_3O_3S$ requires 226.6521).
25. Part of this work was presented at *'Le Défi des Nouvelles Technologies en Chimie Moléculaire'*, Université de Rennes 1, Campus de Beaulieu, France, 15-18 Avril 2002, Poster Abstracts, P-4, see site http://ntc2002.univ-rennes1.fr
26. When the same reaction mixture was heated in an oil bath previously set at the same boiling point for the same reaction time, the yields were lower (**8a:** 85% in oil bath and 88% under microwave).
27. The new 5-alkylaminomethylidene-3-alkyl-2-thioxo-imidazolidin-4-ones **8**, **10** and **12** will be evaluated in a drug discovery program (protein kinase C inhibition activities) at the 'Station Biologique de Roscoff, BP 74-29682 Roscoff Cedex, France'.