

SYNTHESIS OF NEW 5-BROMO-1H-INDOLE-2,3-DIONE DERIVATIVES BY 1,3-DIPOLAR CYCLOADDITION

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Abstract

To contribute to the development of the chemistry of 5-bromo-isatin, we have synthesized new heterocyclic systems, using alkylation reactions under conditions of phase transfer catalysis to be then subjected to cycloaddition reactions dipolar involving 1,3-dipoles.

The structures of the various products obtained were determined by ¹H NMR, ¹³C NMR spectroscopy.

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Received 13 Jan 2017,

Revised 25 Feb 2017,

Accepted 01 April 2017

Keywords: 5-bromoisatin, 1,3-dipolar cycloaddition, dipolarophile, heterocyclic.

Introduction

Given the biological interest of heterocyclic compounds, we have been interested in synthesizing new polyfunctional heterocyclic systems capable of presenting potential applications. Then, we acceded to the 1,3-dipolar cycloaddition reaction with the alkylated 5-bromoisatin molecule. The reaction of the 1,3-dipolar cycloaddition is a method for the synthesis of pentagonal rings in cyclic and heterocyclic compounds [1-3]. This reaction is also used for the synthesis of natural products such as sugar derivatives [4], β -lactams [5], amino acids [6], alkaloids [7, 8] and products with pharmacological interest such as Pyrazolines which have several biological activities [9-11]. This type of reactions depends on a 1,3 dipole which is added to multiple link systems (alkynes, olefin derivatives) or dipolarophiles, to form a 5-membered ring according to the 1,3-dipolar cycloaddition. The general application of 1,3-dipoles in organic chemistry was first established by Huisgen in 1960, as a zwitterionic resonance structure carrying a negative charge located on the end of the bond, which reacts with an unsaturated system (dipolarophile) to form a pentagonal cycloadduct [12]. In this work we will present an overview of the main methods of preparation of the heterocyclic derivatives, by applying the 1,3-dipolar cycloaddition reaction between the 1,3-dipoles and the dipolarophile which has already been synthesized by the reaction of *N*- Alkylation under the conditions of phase transfer catalysis.

Experimental part:

NMR (^1H and ^{13}C) spectra were recorded on a Bruker Avance 300 and 400 MHz spectrometer in a CDCl_3 solution, with tetramethylsilane (TMS) as the internal standard ($\delta=0$). The chemical displacements are presented in part per million (ppm), the coupling constants (J) are expressed in hertz. And the melting points were determined by the Kolfer Bench apparatus.

Synthesis of Compound 1

To a solution of 5-bromo-1*H*-indole-2,3-dione (0.4 g, 1.76 mmol) and DMF (15 mL), the allyl bromide reagent (0.16 mL, 1.38 mmol) was added in stoichiometric amount, in the presence of potassium carbonate (0.6 g, 4.4 mmol) and tetra-*n*-butylammonium bromide (0.1 g, 0.4 mmol). The mixture was stirred at room temperature for 48 h. The reaction was monitored by thin layer chromatography, then the solution was filtered and the solvent removed in vacuo. The mixture obtained is chromatographed on a silica gel column (eluent Hexane / Ethyl acetate), and the final product is recrystallized from analytical ethanol.

1-allyl-5-bromoindoline-2,3-dione : 1

Yield = 87% ; $F(\text{°C}) = 171-175$; $R_f : 0.79$ (Hexane/EtOAc : 2/1); ^1H NMR (CDCl_3 ; 300MHz): $\delta(\text{ppm})$ 7.66 (1H, d, $^4J = 2.46$ Hz); 7.62 (1H, dd, $^3J = 10.44$ Hz); 6.75 (1H, d, $^3J = 8.34$ Hz); 5.72 (1H, m) ; 5.22 (2H, m), 4.3 (2H, t, $^3J = 5.37$ Hz). ^{13}C NMR (CDCl_3 ; 75MHz): $\delta(\text{ppm})$ 178.3 (-C=O); 156.1 (N-C=O); 148.1 (Cq); 140.5 (CH_{Ar}); 130.4 (CH_{Ar}); 128.1 (CH_{Ar}); 120.8 (Cq); 119.1 (C-Br); 112.6 (CH); 103.1 (CH_2); 42.5 (CH_2).

Synthesis of Compound 2-7

In a flask, (0.2 g, 0.75 mmol) of 1-allyl-5-bromoindoline-2,3-dione **1**, and 1.2 equivalents of the alkylating agent are dissolved in 15 ml of dichloromethane, with vigorous stirring we add sodium hypochlorite solution at 0 °C. Stirring is continued for 4 hours. The reaction is monitored by thin layer chromatography, then the solution is filtered and the solvent is removed in vacuo. The mixture obtained is chromatographed on a silica gel column (eluent Hexane / ethyl acetate).

5-bromo-1-((3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)indoline-2,3-dione : 2

Yield= 32% ; F(°C) = 190-195 ; R_f : 0.51 (Hexane/EtOAc : 1/1) ; ¹H NMR (CDCl₃; 400MHz): δ (ppm) 7.63-7.73 (4H, m); 7.40-7.43 (3H, m); 7.16 (1H, d, ³J= 8.4 Hz); 5.08 (1H, m); 3.92-4.08 (2H, m); 3.54 (1H, dd) ; 3.26 (1H, dd). ¹³C NMR (CDCl₃; 75MHz): δ (ppm) 172.5 (C=O); 158.9 (N-C=O); 151.5, 143.5, 127.1 (Cq); 135.5, 125.2, 121.8, 120.5, 109.1, 105.2 (CH_{Ar}); 114.8 (C-Br); 56.1 (CH); 49.8, 37.8 (CH₂).

5-bromo-3'-phenyl-1-((3-phenyl-4,5-dihydroisoxazol-5-yl) methyl) spiro [indoline-3,5'-[1,4,2]dioxazol]-2-one : 3

Yield = 24% ; F(°C) = 201-207 ; R_f : 0.42 (Hexane/EtOAc : 1/1) ; ¹H NMR (CDCl₃; 400MHz): δ (ppm) 7.76 (1H, m); 7.33-7.55 (10H, m); 7.08 (1H, d, ³J= 8.16 Hz); 4.99 (1H, m); 3.74-3.97 (2H, m); 3.15-3.41 (2H, m). ¹³C NMR (CDCl₃; 75MHz): δ (ppm) 184 (C=O); 162.1 (N-C=O); 151.2 (N-C-O); 149.3, 131.4, 129.8 (Cq); 143.8, 120.3, 119.5, 118.1, 118, 117.9, 117.6, 116.8, 114.5, 112.3, 112.1 (CH_{Ar}); 118.4 (C-Br); 51.9 (CH); 48.2, 41.3 (CH₂).

5-bromo-1-((3-(4-chlorophenyl)-4,5-dihydroisoxazol-5-yl) methyl) indoline-2,3-dione : 4

Yield = 34%; F(°C) = 180-184 ; R_f : 0.4 (Hexane/EtOAc: 1/1); ¹H NMR (CDCl₃; 400MHz): δ (ppm) 7.05-7.67 (6H, m); 4.97-5.04 (1H, m); 3.84-3.9 (1H, m); 3.38-3.42 (1H, m); 3.19-3.13 (1H, m). ¹³C NMR (CDCl₃; 75MHz): δ (ppm) 181.6 (C=O); 161.9 (N-C=O); 158.1, 149.1, 131.4 (Cq); 137.1 (C-Cl); 135.4, 130.4, 130.1, 129.8, 129.5, 123.9, 118.7 (CH_{Ar}); 115.2 (C-Br); 60.5 (CH); 51.2, 48.7 (CH₂).

5-bromo-1-((3-(4-chlorophenyl)-4,5-dihydroisoxazol-5-yl)methyl)-3'-phenylspiro[indoline-3,5'-[1,4,2]dioxazol]-2-one : 5

Yield = 21% ; F(°C) = 194-198 ; R_f : 0.33 (Hexane/EtOAc : 1/1) ; ¹H NMR (CDCl₃; 400MHz): δ (ppm) 7.42-7.58 (4H, m); 7.37-7.4 (4H, m); 7.28-7.32 (3H, m); 4.41 (1H, m); 4.05 (2H, m); 3.67 (2H, m). ¹³C NMR (CDCl₃; 75MHz): δ (ppm) 174.4 (C=O); 161.3 (N=C-O); 154.6, 147.3, 124.5, 123.8, 118.6 (Cq); 138.2 (C-Cl); 136.4, 131, 129.4, 129.1, 128.9, 128.4, 127.2, 126.8, 119.1 (CH_{Ar}); 120.2 (C-Br); 62.7 (CH); 59.2, 54.7 (CH₂).

5-bromo-1-((3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl) methyl) indoline-2,3-dione : 6

Yield = 32% ; F(°C) = 201-205 ; R_f : 0.38 (Hexane/EtOAc : 1/1) ; ¹H NMR (CDCl₃; 400MHz): δ (ppm) 8.11-8.20 (1H, m); 7.56-7.78 (3H, m); 6.78-7.08 (3H, m); 5.80-5.87 (1H, m); 5.29-5.35 (2H, m); 4.33-4.4 (2H, m); 3.86-3.93 (3H, m). ¹³C NMR (CDCl₃; 75MHz): δ (ppm) 186.1 (N-C=O); 168.1 (N=C-O); 163 (C-O); 157.2, 138.2, 133.7 (Cq); 146, 129.3, 128.3, 127.3, 125.9, 123.9, 121.9 (CH_{Ar}); 111.3 (C-Br); 56.5 (CH); 42.7, 41.1 (CH₂); 33.1 (CH₃).

5-bromo-1-((3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl) methyl)-3'-phenylspiro[indoline-3,5'-[1,4,2]dioxazol]-2-one : 7

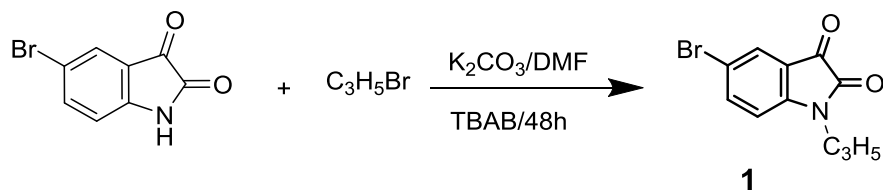
Yield = 29% ; F(°C) = 210-216 ; R_f : 0.2 (Hexane/EtOAc : 1/1) ; ¹H NMR (CDCl₃; 300MHz): δ (ppm) 7.6-7.78 (2H, m); 7.56-7.60 (5H, m); 7.12-7.19 (1H, m); 6.91-6.96 (3H, m); 5.04 (1H, m); 3.82-3.97 (7H, m) ; 3.2-3.45 (2H, m). ¹³C NMR (CDCl₃; 75MHz): δ (ppm) 175.2 (C=O); 166.9 (C-O); 159.7 (N=C-O); 155.5, 132.6, 124.6 (Cq); 142.1, 112.9, 112.1, 107.1, 105.8, 103.4, 102.3, 101.4 (CH_{Ar}); 119.2 (C-Br); 59.4 (CH); 50.6 (CH₃); 45.7, 45.2 (CH₂).

Results and discussions

We are interested in the reactivity of nitriloxides with exocyclic carbon-carbon double bonds, it is carried out in the presence of a dipolarophile and a 1,3-dipole. First, 1-allyl-5-bromoindoline-2,3-dione (**1**) was synthesized using the *N*-alkylation method involving 5-bromo-1*H*-indole-2,3-dione with 1.1 equivalent of alkylating agent under the

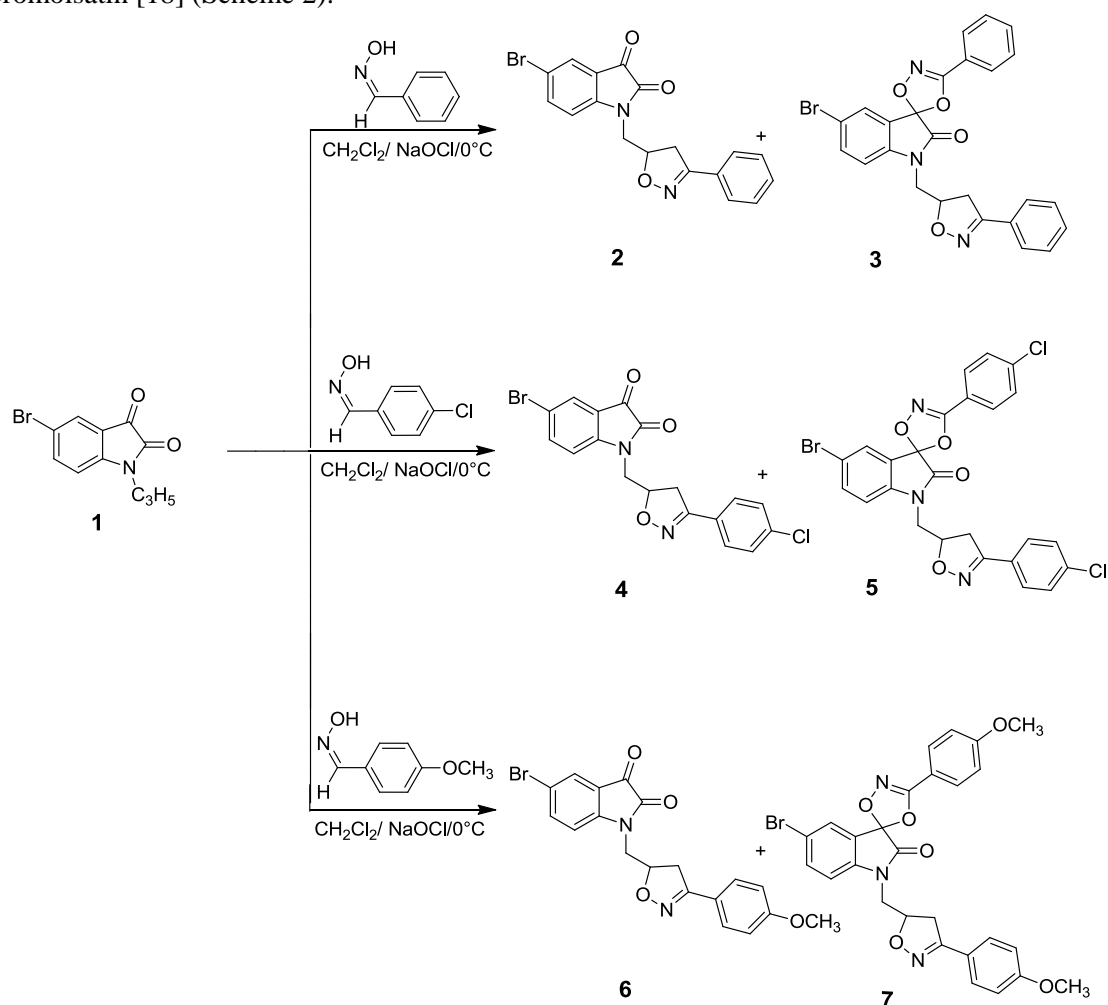
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conditions of phase transfer catalysis with the presence of tetra-*n*-butylammonium bromide (BTBA) as catalyst [13-15], after treatment of the reaction, compound **1** was obtained in good yield (Scheme 1).



Scheme 1: Synthesis of 1-allyl-5-bromoindoline-2,3-dione.

The 1,3-dipolar cycloaddition reaction [16,17] between the 1-allyl-5-bromoindoline-2,3-dione (**1**) obtained by reaction of *N*-alkylation and the oxime, leads to two cycloadducts in good yield. The first compound results from dipolar cycloaddition affecting the allyl chain at position 1 of 5-bromoisatin, and the second compound is derived from a dipolar cycloaddition on the carbon-oxygen double bond in position 3, and dipolar cycloaddition affecting the allyl chain of 5-bromoisatin [18] (Scheme 2).



Scheme 2: 1,3-dipolar cycloaddition of 1-allyl-5-bromoindoline-2,3-dione.

¹H-NMR spectrums of compounds (**1-4**) and (**6-7**) are showed below (Figure 1). The allylic proton of compound **1** resonated at 5.80-5.69 ppm as a multiple.

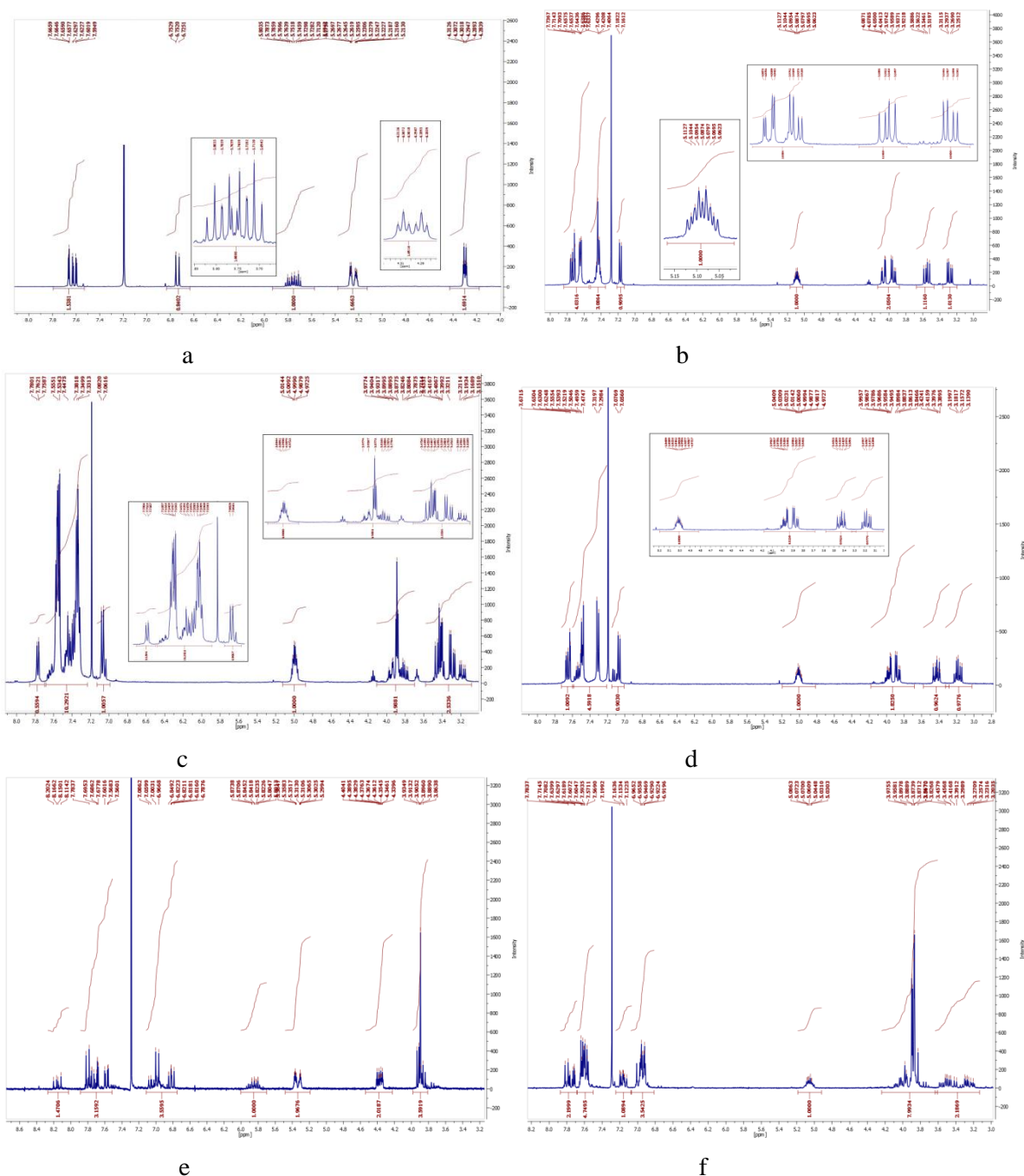


Figure 1: ^1H -NMR spectra of compounds (1-4) and (6-7) (a-f) respectively.

Conclusion

In this work we were able to prepare new compounds according to the 1,3-dipolar cycloaddition reaction on the dipolarophile group of 5-bromoisatin, this reaction allowed us to synthesize new heterocyclic systems associating different atoms. The selectivity of the dipoles is remarkable towards the two dipolarophilic sites. The first reaction results from a dipolar cycloaddition affecting the allyl chain at position 1 of 5-bromoisatin, and the second results from a dipolar cycloaddition on the carbon-oxygen double bond in position 3, and a dipolar cycloaddition affecting the allyl chain at position 1 of 5-bromoisatin.

References:

- [1] A. Padwa, « In 1,3-Dipolar Cycloaddition Chemistry »; Wiley-Interscience: New York, 1 1984.
- [2] D. P. Curran. Ed. Advances in Cycloaddition; JAI: Greenwich., 1 (1988) 1990.
- [3] A. Padwa, Intermolecular 1,3-Dipolar Cycloaddition. In Comprehensive Organic Synthesis; B. Trost, I. M. Fleming, Eds.; Pergamon: Oxford, 4 (1991) 1069.
- [4] P. De Shong, J. M. Leginus, S. W. Lander, *J. Org. Chem.*, 51 (1986) 574.
- [5] T. Kametani, S.-D. Chu, T. Honda. *J. Chem. Soc. Perkin. Trans.*, 1 (1988) 1598.
- [6] R. Annuziata, M. Chinquini, F. Cozzi, L. Raimondi. *Tetrahedron.*, 43 (1987) 4051.
- [7] J. Tufariello. *J. Acc. Chem. Res.*, 11 (1979) 369.
- [8] S. A. Ali, J. H. Khan, M. I. M. Wazeer, *Tetrahedron.*, 44 (1988) 5911.
- [9] Elugero. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford 1984.
- [10] N. Araino, J. Miura, Y. Oda, H. Nishioka, *Chem. Abstr.*, 125 (1996) 300995.
- [11] C. R. Harrison, R. M. Lett, S. F. Mccann, R. Shapiro, T. M. Stevenson. *Chem. Abstr.* 124 (1996) 202246.
- [12] R. Huisgen, *Angew. Chem.*, 75 (1963) 604.
- [13] Y. Kharbach, A. Haoudi, F. Capet, A. Mazzah, L. El Ammari. *Acta Cryst.* 71 (2015) 1024-1025
- [14] Z. Tribak, Y. Kandri Rodi, Y. Kharbach, A. Haoudi, M.K. Skalli, A. Mazzah, M. Akhazzane, E.M. Essassi. *J. Mar. Chim. Heterocycl.* 15 (1) (2016) 79-84.
- [15] Y. Kharbach, A. Haoudi, Y. Kandri Rodi, M. K. Skalli, A. Mazzah, E.M. Essassi. *J. Mar. Chim. Heterocycl.* 14 (1) (2015) 63-68.
- [16] Y. Ben Dhia , J. P. Praly, *J. Mar. Chim. Heterocycl.* 6 (2007) 13-20.
- [17] U. Chiacchio, A. Corsaro, D. Iannazzo, A. Piperno, A. Procopio, A. Rescifina, G. Romeo, R. Romeo, *Eur. J. Org. Chem.* (2001) 1893.
- [18] K. Attar, M. Benchidmi, E. M. Essassi. *J. Mar. Chim. Heterocycl.* 13 (2014) 48-52.