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One-pot regioselective synthesis of n-benzoyl 2-amino-3,4-dihydro-3-oxo-2h-1,4-benzothiazines

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ABSTRACT

A protocol for regioselective one-pot synthesis of 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazines has been developed. Starting from commercially available 2-aminothiophenols, a base-mediated regioselective S-alkylation took place with methyl α-azido glycinates to give the acyclic intermediates, which underwent spontaneously an intramolecular amidation reaction to furnish 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazines in 68% yields.

Key words: amino acids, methyl α-azido glycinate, 2-aminothiophenol, *S*-alkylation, *N*-alkylation, N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazines.

INTRODUCTION

Nitrogen-containing heterocycles are undoubtedly one of the most important targets in organic chemistry. They are widely distributed in natural products and in pharmaceutical agents and numerous studies for their chemistry and synthesis have been reported[1]. Consequently new reactions, in which nitrogen-containing heterocycles can be prepared in a chemo- and stereoselective way, will be broadly applicable for endeavours in natural product synthesis and medicinal chemistry.

The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities: antitumoral[2,3], antimicrobial[4], antitubercular[5], antimalarial[6], and antibacterial[7].

As part of our program aimed at the synthesis and biological evaluation of heterocyclic compounds[8], and consistent with the previous studies, and in view of the continuous interest for new antimicrobial agents, we deemed it worthwhile to synthesize the product N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1 ,4-benzothiazine and seek the biological activity of the molecule.

Various benzothiazine derivatives are known to possess a versatile range of biological activities and have been synthesized continuously since the very first synthesis by Abe *et al.*[9]. Among these, 1,2-benzothiazine-3-carboxamide-1,1-dioxides such as Piroxicam[10], Ampiroxicam[11] and Meloxicam[12] are familiar for their analgesic and anti-inflammatory activities and are being used worldwide as non-steroidal anti-inflammatory drugs (NSAIDs). Some of the 3,4-dihydro-1,2-benzothiazine-3-carboxylate 1,1-dioxide a-ketomide and P(2)–P(3) peptide mimetic aldehyde compounds act as potent calpain I inhibitors[13] while 1,2-benzothiazin-3-yl-quinazolin-4(3H)-ones possess antibacterial properties[14].

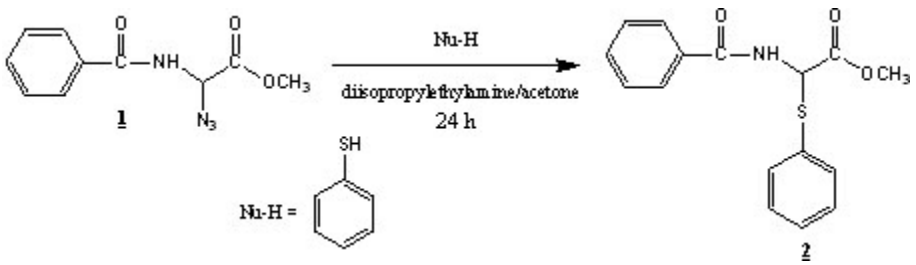
Continued our investigations on the use of organic azides[15] in heterocyclic synthesis, we reported in this paper another part of our investigations concerning the preparation of new heterocyclic carboxylic compounds. Azide derivative **1** was prepared using Steglich method[16] and Achamlale's procedure[17].

Methyl α-azido glycinate *N*-benzoylated **1** was obtained by the reaction of sodium azide with the methyl α-bromo glycinate. The title compound is stable and can be stored for an unlimited time without any signs of decomposition. The methyl α-bromo glycinate also can be used and gives satisfactory results; the azide **1** is used especially for its stability.

RESULTS

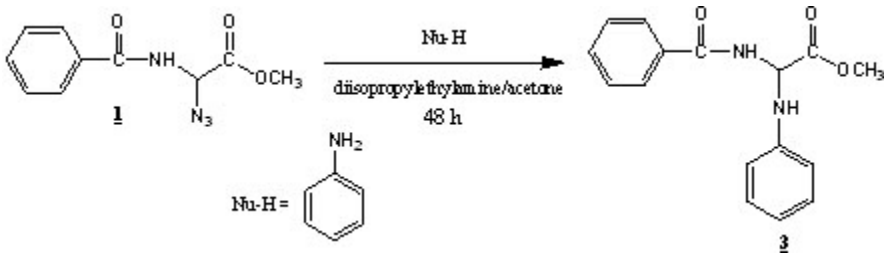
To understand the results of the reaction of 2-aminothiophenol with azide 1, we performed the reaction of N-alkylation of aniline and S-alkylation of the thiol with azide 1.

The S-alkylation of thiophenol by amino ester 1 is performed in presence of diisopropylethylamine in acetone at room temperature for 24 hours. The yield is 82% after purification of the crude reaction mixture by column chromatography on silica gel eluted with hexane / ether 1/1 (scheme 1).



Scheme 1

Under the conditions specified above, the N-alkylation of aniline by the methyl α- azidoglycinate N-benzoylated 1 leads, after a reaction time of 48 hours to the desired product 3. After purification of the crude reaction mixture by column chromatography on silica gel (eluent: hexane / ether: 1 / 1), compound 3 was isolated in pure form a white solid with a yield of 80% (scheme 2).

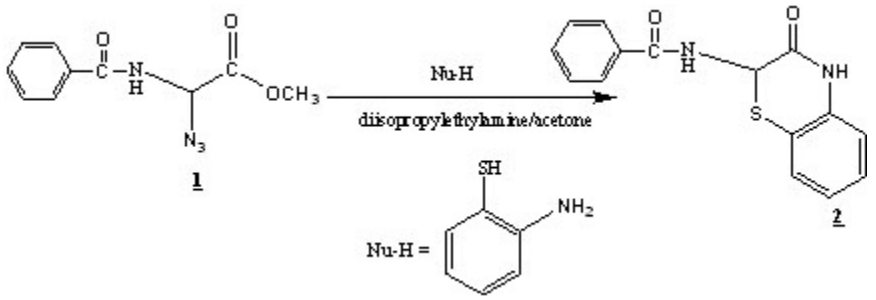


Scheme 2

By comparing the reactivity of both nucleophiles towards the azide 1, the reaction yield of aniline is lower than the reaction of the thiol. Time of the reaction of S-alkylation is faster than that of the N-alkylation. This can be justified given that the sulfur atom is more polarizable than the nitrogen atom. To exploit these results, we conducted the reaction of 2-aminothiophenol with azide 1. Our

strategy is based on the S-alkylation of 2-aminothiophenol with methyl α-azido glycinate 1 (Scheme 3).

S- and N-alkylation and S-alkylation is predominant. The spectroscopic data obtained showed a single product by regioselective reaction in one step.



Scheme 3

The reaction of 2-aminothiophenol on azide derivative 1 result in compounds 4.

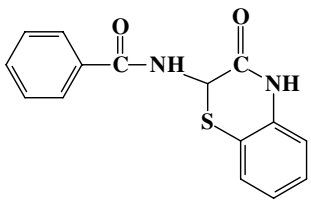
The literature reports numerous methods of a regioselective one-pot synthesis[18]. The reaction was carried out in dry acetone at room temperature in presence of diisopropylethylamine. Results are summarized in Table 1.

The products **4** were obtained with 68% from **1** and were analyzed by MS, ^{13}C NMR, ^{1}H NMR and ^{15}N NMR.

EXPERIMENTAL

Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. NMR spectra (1H, ^{13}C, ^{15}N) were recorded on a Bruker AM 300 (operating at 300.13 MHz for ^{1}H, at 75.47 MHz for ^{13}C, at 30.41 MHz for ^{15}N) spectrometer (Centre Universitaire Régional d'Interface, Fès). NMR data are listed in ppm and are reported relative to tetra-methylsilane (^{1}H, ^{13}C); residual solvent peaks being used as internal standard. All reactions were followed by TLC. TLC analyses were carried out on 0.25 mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F254) and spots were visualised under UV light or by exposure to vaporised iodine. Mass spectra were recorded by electrospray on a micromass ESI Platform II (Université Montpellier II, France) and on a PolarisQ Ion Trap GC/MSn Mass Spectrometer (Centre Universitaire Régional d'Interface, Fès). Methyl α-azido glycinate **1** was prepared using Achamlale's method[16].

Table 1: Synthesis of N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 2

Product	Nu-H	M.P. (°C)	Reaction Time (h)	Yield (%)
	2-aminothiophenol	228-230	48	68

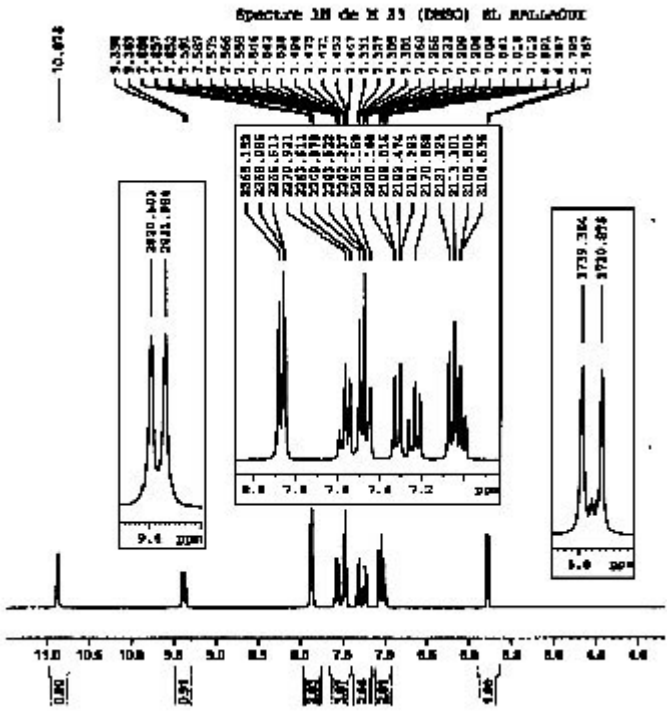


Fig. 1: NMR spectra ^{1}H of N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 4

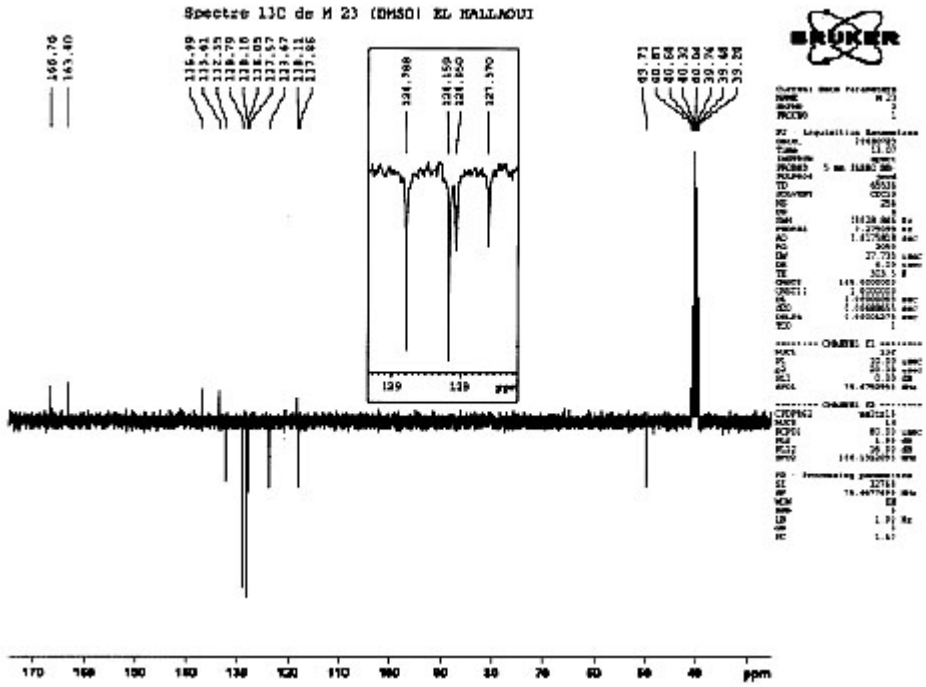


Fig. 2: NMR spectra ^{13}C of N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 4

Typical procedure for *N*-alkylation

To a stirred solution of 2.86 mmoles of 2-aminothiophenol and 3.12 mmoles of diisopropylethylamine in 10 ml of dry acetone, 2.6 mmoles of α-azido glycinate were added. The mixture was stirred at room temperature and the reaction was followed by TLC (Kiesegel Merck 60F524). The solvent was evaporated under reduced pressure. The residue was quenched with saturated aqueous solution of ammonium chloride (20 ml) and extracted with dichloromethane (20 ml × 3). The organic phase was dried in sodium sulfate (Na_2SO_4) and the solvent was removed under reduced pressure. The product was purified by

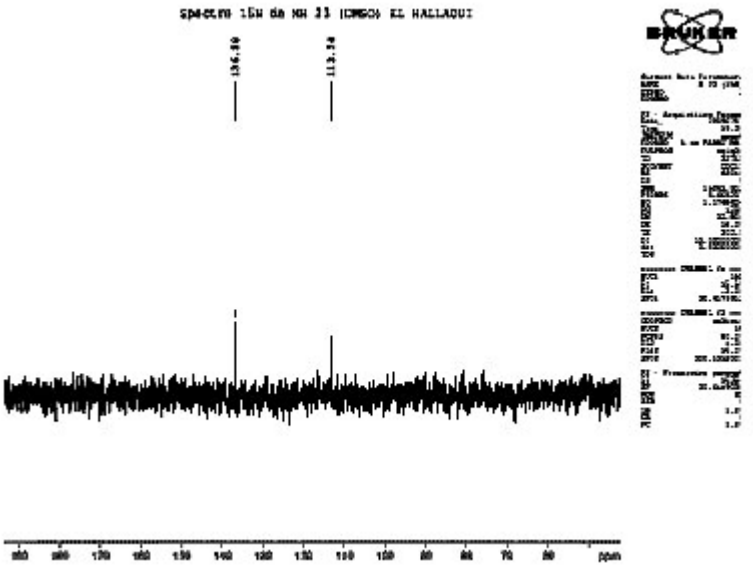


Fig. 3: NMR spectra ^{15}N of N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 4

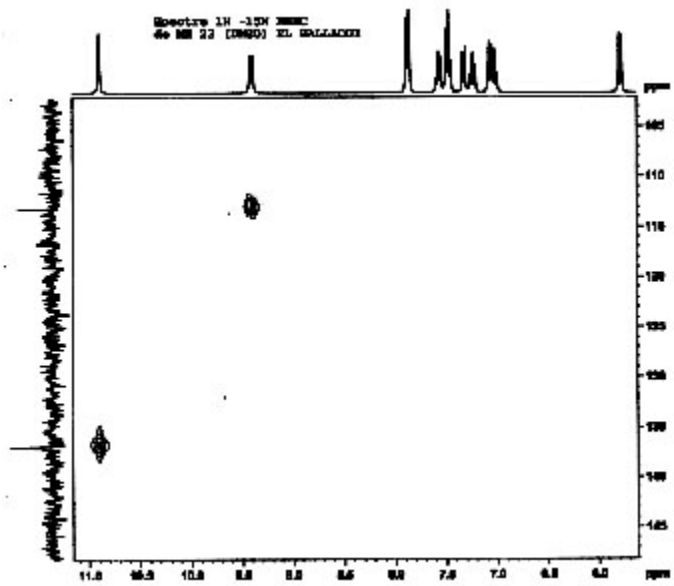


Fig. 4: HMBC ^{1}H – ^{15}N spectra of N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 4

column chromatography on silica gel using ether/ hexane as eluant to afford pure S-alkylated and N-alkylation product.

Methyl 2-benzamido-2-(phenylsulfanyl) acetate 2

Yield: 82 %; mp: 76-78 °C (ether/ hexane); Rf: 0.8 (ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ : 3.821 (3H, s, OCH_3); 5.9 (1H, d, *J* = 8.5 Hz, H_α); 6.9 (1H, d, *J* = 8.5 Hz, NH); 7.36-7.8 (10H, 2m, H_{arom}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ : 53.05 (CH_3O); 56.71 (-CH-); 127.11 (2C), 128.71 (2C), 129.22 (2C), 129.65, 129.85, 132.19, 133.22, 135.74 (2C) (C_6H_5 aromatic carbons); 165.76, 169.16 (2CO).

MS-EI: 604.4 [2M+1], 301.8 [M]; $C_{16}H_{15}NO_3S$.

Methyl 2-benzamido-2-(phenylamino)acetate 3

Yield 80 %; Solid, m.p.124-126 (ether/ hexane); Rf = 0.75 (ether); ^{1}H-NMR ($CDCl_3$, ppm): δ: 3.87 (3H, s, OCH_3); 4.9 (1H, br s, NH), 6.2 (1H, d, *J* = 8 Hz, H_α), 6.68-7.8 (11H, 4m, H_{arom} + NH_{amid}).

^{13}C-NMR ($CDCl_3$, ppm): δ: 5 3.00 (CH_3O); 60.9 (-CH-); 113.5 (2C), 118, 127.9 (2C), 128.80 (2C), 129.4, 132.2 (2C), 133.7, 146.2 (C_6H_5 aromatic carbons); 166.7, 170 (2CO).

MS (electrospray) m/z: 285.2 [M+1]; $C_{16}H_{16}N_2O_3$.

N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 4

yield : 68%; mp: 228-230 (ether / hexane); R_f: 0.4 (ether) ^{1}H NMR ($DMSOd_6$): δ: 5.8 (1H, d, *J* = 8.5Hz, H_δ); 7 (2H, m, H_{arom}); 7.2-7.9 (7H, m, H_{arom}); 9.4 (1H, d, *J* = 8.5 Hz, NH_{amide}); 10.9 (1H, s, NH_{amide}).

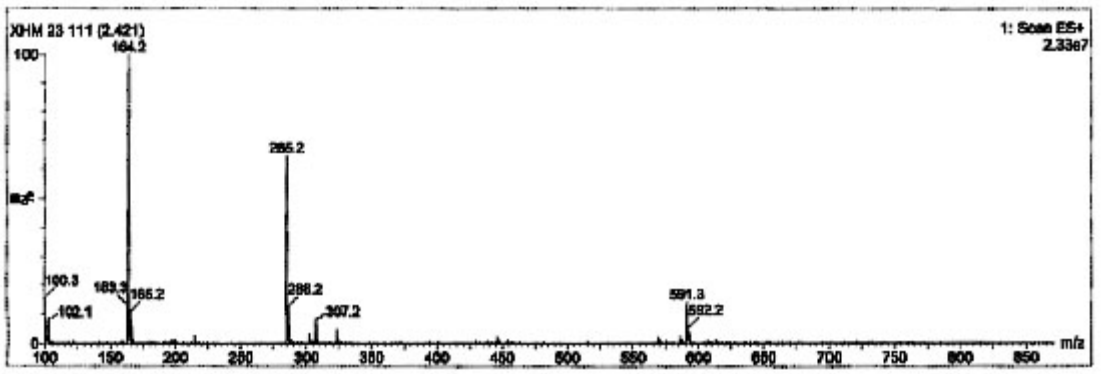


Fig. 5: Mass spectra of N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 4

^{13}C NMR ($DMSOd_6$): δ: 49.71 (-CH-); 117.86, 118.11, 123.67, 127.57, 128.05, 128.16 (2C), 128.79 (2C), 132.35, 133.61, 136.99 (C_6H_5 aromatic carbons); 163.40, 166.75 (2CO).

^{15}N NMR ($DMSOd_6$): δ: 113.24, 136.88.

M.S. (electrospray): [M^+] = 285.2; [$M+H^+$] = 286.2; [$M+Na^+$] = 307.2; [$2M+Na^+$] = 592.2; $C_{15}H_{12}N_2O_2S$.

CONCLUSION

In conclusion, this method provides general and convenient access to a wide range of N-benzoyl 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazines derivatives starting from the appropriate azide derivative **1**. A base-mediated regioselective S-alkylation took place with methyl ±-azido glycinates to give the acyclic intermediates, which underwent spontaneously an intramolecular amidation reaction occurred under very mild conditions and led to desired products with good yields.

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