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Reaction of 2-aminothiophenol with 2,5-dihydro-2,5-dimethoxyfuran : a facile route to a new dihydrobenzothiazine derivative

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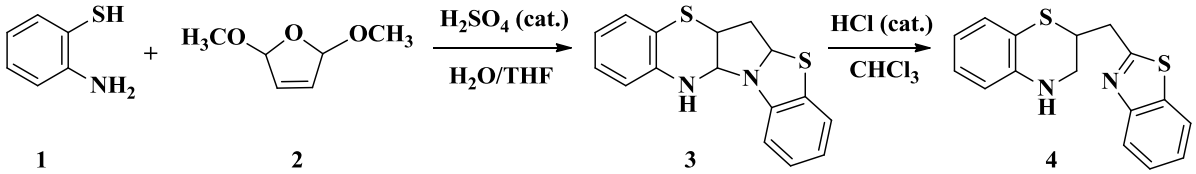
Abstract: As part of our studies focused on the design and synthesis of biologically active molecules, polyheterocyclic compound **3** was prepared in one step from commercially available 2-aminothiophenol **1** and 2,5-dihydro-2,5-dimethoxyfuran **2**. Derivative **3** underwent a further isomerization to compound **4** in a reaction promoted by traces of HCl in chloroform.



Keywords: Aminothiophenol, Dihydrobenzothiazines, Dihydrodimethoxyfuran, Fumaraldehyde.

Introduction

1,4-Benzothiazines are known to possess a wide spectrum of biological and pharmacological activities[1]. These compounds have been prepared by a variety of methods[2]. One of them uses 2-aminothiophenol and different carbonyl derivatives as starting materials and it has been studied extensively[3]. The course of the reaction was found to depend on the conditions, as well as the nature of the carbonyl derivatives. Benzothiazoles, benzothiazepines, as well as other ring systems have also been obtained by this reaction.[3]

As part of our studies focused on the synthesis of new benzothiazines, we became interested in the new functionalized derivative **5** since both the aldehyde function and the secondary amine would be useful handles to prepare chemical libraries starting from such an intermediate. Following literature data, this compound should be accessible in principle by reaction of 2-aminothiophenol with a 1,4-dialdehyde, such as fumaraldehyde or equivalent derivatives (Scheme 1)

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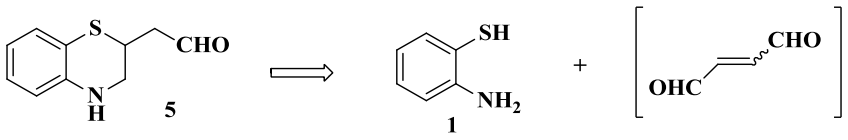
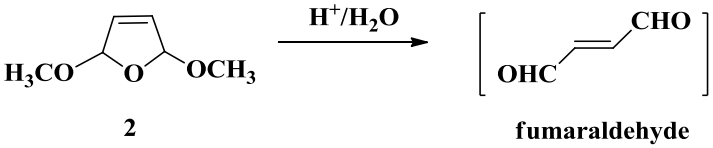


Scheme 1. Retrosynthetic analysis for compound **5**.

Therefore, we have studied the reaction of 2-aminothiophenol **1** with 2,5-dihydro-2,5-dimethoxyfuran **2**, as precursor (*in situ*) of the α,β-unsaturated dicarbonyl system, namely the unstable fumaraldehyde[4] (Scheme 2).

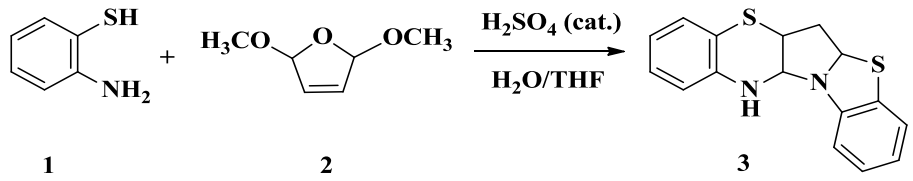


Scheme 2. Generation of fumaraldehyde *in situ* from 2,5-dihydro-2,5-dimethoxyfuran.

Unexpectedly, the reaction did not give the desired dihydrobenzothiazine product **5**. Instead, it led to the formation of a stable crystalline polycyclic compound **3**. The structure and the stereochemistry of compound **3** were established using spectral techniques and confirmed by X-ray crystallography.[5] To the best of our knowledge, only one example of polycyclic compound of this type has been reported to date[6]. Further, compound **3**, once dissolved in $CHCl_3$ with traces of acid, underwent isomerization to a new dihydrobenzothiazine-benzothiazole system **4**.

Results and Discussion

Reaction of 2,5-dihydro-2,5-dimethoxyfuran **2** with an excess of 2-aminothiophenol **1** (2.5 equiv.) in a THF/H_2O mixture in the presence of a catalytic amount of conc. H_2SO_4 at room temperature gave the compound **3** in 50% yield, as a crystalline solid (Scheme 3).



Scheme 3. Preparation of compound **3**.

The same reaction has been performed using dimethyl acetal of fumaraldehyde (another precursor of fumaraldehyde) instead of **2**, but it resulted in a considerable decrease in the yield of compound **3** (15 - 20% yield).

The structure of compound **3** was established on the basis of extensive 1D- and 2D-NMR studies and confirmed by X-ray crystallography (Figure 1). In the ^{1}H NMR spectrum of **3**, the triplet at δ 5.80 ppm (J = 4.9 Hz) has been assigned to the proton H_{16} and the doublet at δ 4.91 ppm (J = 5.7 Hz) assigned to proton H_8, the triplet of doublets signal at δ 3.91 ppm (J = 7.4 Hz and J' = 5.7 Hz) attributed to proton H_{18}, the doublet of doublets signal at δ 2.57 ppm (J = 7.4 Hz and 4.9 Hz) attributed to the two diastereotopic protons H_{17} and $H_{17'}$ which seem to be

equivalent because they have similar environment. It is important to note that H_8 couples with H_{18} with a coupling constant J = 5.7 Hz which is indicative of a *cis* relationship. This stereochemical *cis* relationship between protons H_8 and H_{18} is clearly shown in the X-ray of compound **3** (Figure 1). The ^{1}H NMR spectrum of compound **3** also displayed signals in the regions of 6.60-7.20 ppm attributed to the eight protons of the two aromatic rings.

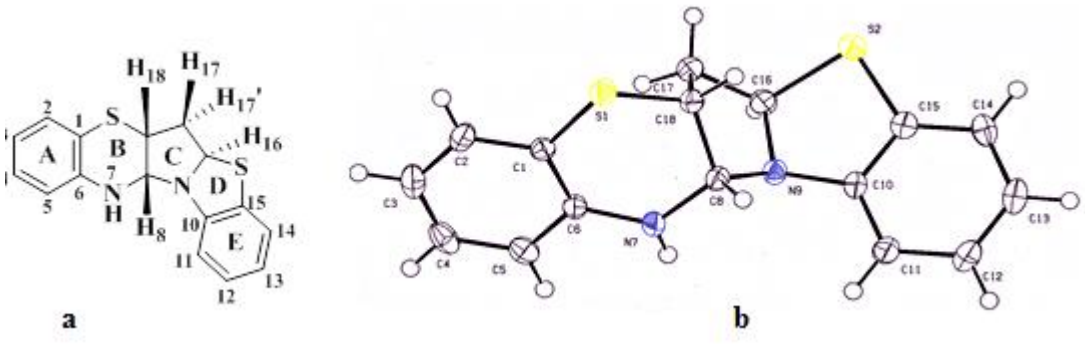
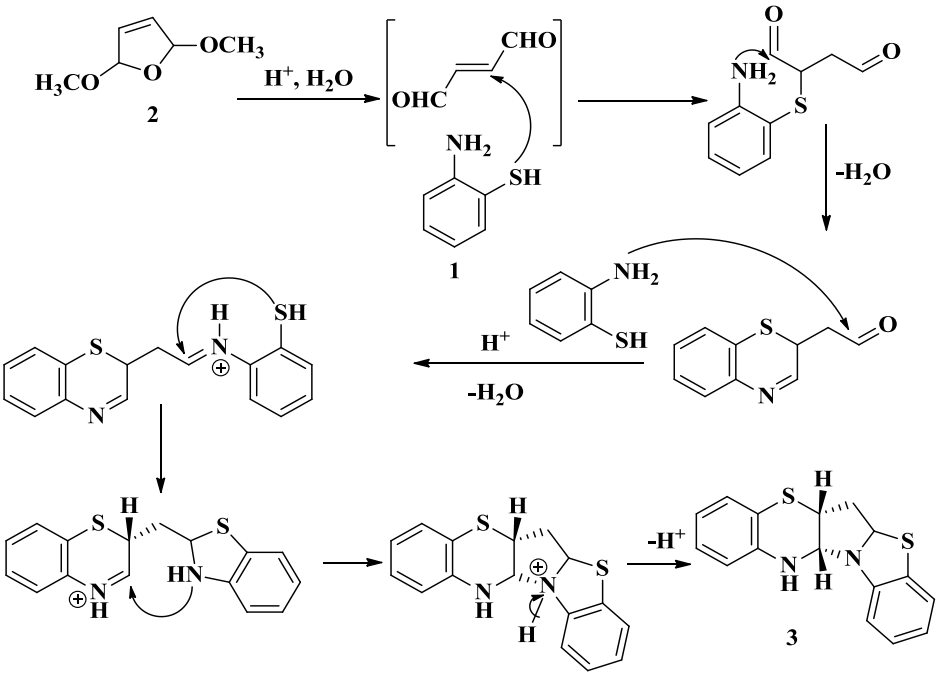


Figure 1. **a**) Structure of compound **3**. **b**) ORTEP X-ray structure of compound **3.**

One interesting feature of this reaction is the stereoselectivity. Compound **3** was isolated as a single diastereoisomer, and we did not observe the formation of another stereoisomer. A tentative mechanism to explain the formation of compound **3** is shown in Scheme 4. It is believed that the first step involves a conjugated addition (Michael addition) of the thiol function on the fumaraldehyde (generated *in situ* from the 2,5-dihydro-2,5-dimethoxyfuran) followed by an intramolecular condensation that leads to the formation of the benzothiazine system. Then, a second molecule of aminothiophenol reacts to give the benzothiazole moiety. The scheme is completed by an intramolecular nucleophilic addition of the benzothiazole nitrogen atom to afford final compound **3**. The transition state leading to a five-membered ring C is believed to be responsible for the observed *cis* stereoselectivity.



Scheme 4. Tentative mechanism for the formation of compound **3**.

We also noticed that, under the same conditions, compound **2** did not react with either 2-aminophenol or 1,2-diaminobenzene, which support our proposed mechanism in which the sulfur atom (soft nucleophile) adds to fumaraldehyde in a 1,4-fashion. This kind of addition is not favoured in case of hard nucleophiles such as NH_2 or OH.

Isomerization:

When compound **3** was dissolved in $CDCl_3$ for a routine ^1H NMR experiment, new signals for aromatic protons appear in the region δ 7.30-8.10 ppm (Figure 2). We suspected a transformation (isomerization) of compound **3**, promoted by trace amounts of acid found in $CDCl_3$, to be taking place in the NMR tube.

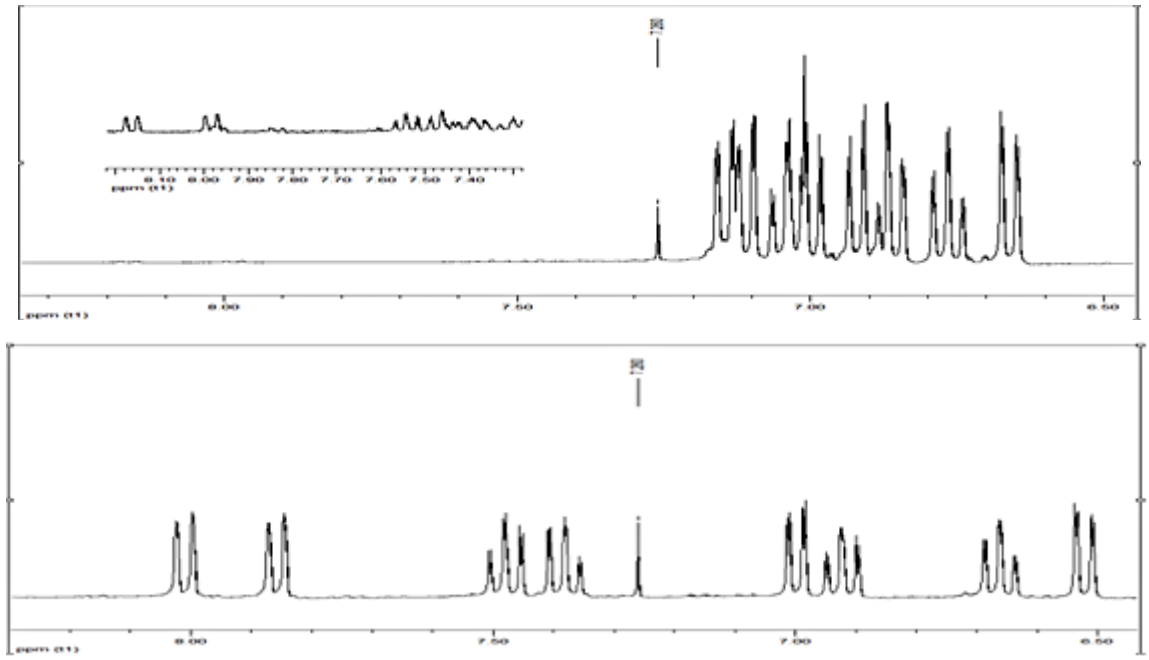
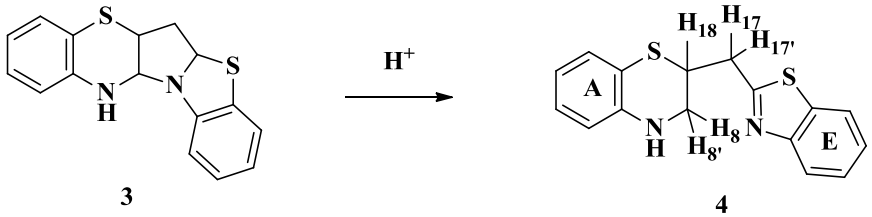


Figure 2. a) Aromatic region of the ^1H NMR spectrum of compound **3** showing the beginning of isomerization to compound **4** taking place in the NMR tube. **b**) Aromatic regions of ^1H NMR spectrum of compound **4** after complete isomerization.

In an attempt to investigate the nature of this transformation, a sample of compound **3** was dissolved in $CHCl_3$ and treated overnight with one drop of concentrated HCl. Complete isomerization to the new compound **4** occurred (Scheme 5).



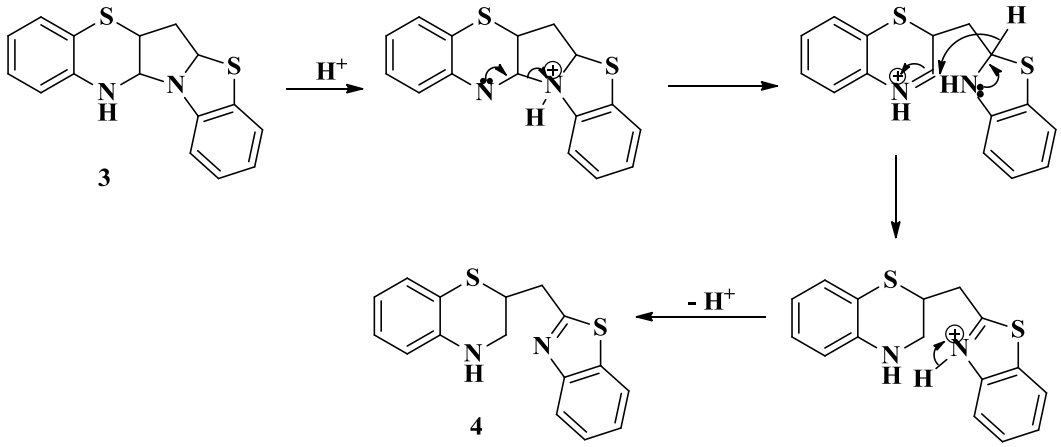
Scheme 5. Isomerization of compound **3** to compound **4**.

The structure of **4** has been proposed based first on the ^1H NMR spectrum which revealed the disappearance of the signal of proton H_{16} at δ 5.80 ppm and the appearance of new signals for aromatic protons in the region δ 7.30-8.10 ppm, characteristics for the benzothiazole

system**.** Further evidence came from the appearance, in the ^{13}C NMR spectrum of compound **4**, of a quaternary carbon signal at δ 167.98 ppm which was assigned to the carbon of C=N. Further evidence for the isomerization was indicated by the high resolution mass spectrum which supported the same molecular formula of $C_{16}H_{14}N_2S_2$ for both compounds **3** and **4**.

The ^1H NMR spectrum of compound **4** also shows many multiplets in the regions of δ 6.50-8.10 ppm attributed to the eight protons of the two aromatic rings. These protons can be divided into two sets: the four protons of the aromatic ring **A** appear in the region of δ 6.50-7.00 ppm (about the same chemical shifts as in compound **3**), and the signals for the four protons of aromatic ring **E** appear at δ 7.40-8.10 ppm. The ^1H NMR spectrum of compound **4** also exhibits many signals in the region from 3 to 4 ppm. A signal (dddd, J = 7.6, 6.9, 5.4, and 2.7 Hz) is seen at δ 3.84 ppm assigned to H_{18}; this proton is coupled to four different protons, the two diastereotopic protons (H_8 and $H_{8'}$) and the two diastereotopic protons (H_{17} and $H_{17'}$) . A doublet of doublet signal at δ 3.71 ppm is attributed to H_8 or $H_{8'}$(J =12.3, 2.7 Hz). Another doublet of doublet at δ 3.56 ppm was assigned to H_{17} or $H_{17'}$ (J =15.0,7.6 Hz. A multiplet is also seen at δ 3.44-3.50 ppm and attributed to two protons [$H_{8(8')}$ and $H_{17(17')}$]. Extensive 2D NMR experiments (COSY, HMQC, HMBC) have been performed on compound **4** and they were in agreement with the proposed structure. Unfortunately, all our attempts to obtain single crystals suitable for X-ray analysis failed.

A tentative mechanism to explain the acid-catalyzed isomerization is shown in scheme 6, and is believed to be driven by the aromatization of the thiazole ring.



Scheme 6: Proposed mechanism for the isomerisation of compound **3** to compound **4**

The fact that isomerization **3** to **4** did not take place in the reaction medium (a THF/H_2O mixture) can be attributed to the low solubility of compound **3** in that medium. It is also important to note that compound **3** was isolated after 24 hours of reaction in THF/H_2O mixture whereas isomerization to compound **4** was complete within few hours in chloroform.

Conclusion

In summary we have described a simple method for the preparation of new polycyclic compounds **3** and **4** which could be of interest in medicinal chemistry. Compound **4** merit special attention since it combines in its structure the two moieties of dihydrobenzothiazine and benzothiazole, which are both recognized as related to a broad range of bioactivities[1,7].

Further studies are currently underway to extend this method to prepare differently substituted polycyclic compounds starting from suitably substituted aminothiophenols.

Acknowledgements

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Experimental Section

The melting points were determined using system Kofler.^{1}H NMR spectra were recorded at 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz. Column chromatography was performed on silica gel, particle size (40-63µm).

Preparation of compound 3*:* To a solution of 2,5-dihydro-2,5-dimethoxyfuran (100 mg, 0.78 mmol) in THF (5 mL) and H_2O (10 mL) was added 2-aminothiophenol (250 mg, 2.0 mmol, 2.5 equiv.). A drop of concentrated H_2SO_4 was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then neutralized with a solution of Na_2CO_3 and extracted with ethyl acetate (3x10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a yellow oil which was purified by column chromatography using hexane-ethyl acetate (98:2) as eluent to give the title compound **3** (114 mg, 50% yield) as a yellowish solid. mp 152-153^{o}C. ^{1}H NMR($CDCl_3$, 300 MHz): δ (ppm) 7.16 (dd; *J* = 7.71, 1.43 Hz; 1H); 7.12 (dd; *J* = 7.52, 1.30 Hz; 1H); 7.06 (td; *J* = 7.76, 1.48 Hz; 1H); 7.01 (dd; *J* = 7.59, 1.41 Hz; 1H); 6.94 (dd; *J* = 7.51, 1.32 Hz; 1H); 6.88 (dd; *J* = 7.66, 1.22 Hz; 1H); 6.78 (td; *J* = 7.54, 1.23 Hz; 1H); 6.69 (dd; *J* = 7.93, 1.18 Hz; 1H); 5.81 (t; *J* = 4.89 Hz; 1H); 4.91 (d; *J* = 5.68 Hz; 1H); 3.91 (td; *J* = 7.42, 5.70 Hz; 1H); 2.57 (dd; *J* = 7.41, 4.90 Hz; 2H).^{13}C NMR ($CDCl_3$, 75 MHz): 147.53(C_{10}); 140.95(C_6); 132.61(C_{15}) ; 116.46(C_1) ; 128.13, 126.61, 125.34, 123.92, 121.93, 119.71, 115.92, and 114.97 (C_2, C_3, C_4, C_5, C_{11}, C_{12}, C_{13}, and C_{14}); 78.76 (CH, C_8); 71.27 (CH, C_{16}); 40.52 (CH, C_{18}); 39.58 (CH_2, C_{17}). HRMS (ESI): $C_{16}H_{14}N_2NaS_2$, $[M+Na]^+$ calcd: 321.04961; found: 321.0494.

***Preparation of compound* 4:** To a solution of **3** (100 mg, 0.34 mmol) in $CHCl_3$ (10 mL) was added one drop of conc. HCl. The reaction mixture was stirred at room temperature overnight. The reaction mixture was then washed with water (3x 5mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a yellow solid which was purified by column chromatography using hexane-ethyl acetate (95:5) as eluent to give compound **4** (98 mg, 98% yield) as a yellowish solid. mp 149-151^{o}C. ^{1}H NMR($CDCl_3$, 300 MHz): δ (ppm) ring E [8.01(d; *J*=7.8 Hz; H_{11} or H_{14}); 7.86 (d; *J*=7.8 Hz; H_{11} or H_{14}); 7.48 (td; *J*=8.11, 1.23 Hz; H_{12} or H_{13}); 7.38 (td; *J*=8.12 , 1.53 Hz; H_{12} or H_{13})]; ring A [7.00 (dd; *J*=7.8 , 1.5 Hz; H_2); 6.93(td; *J*=7.81 *J*=1.53 Hz; H_3); 6.66 (td; *J*=7.82, 1.22 Hz; H_4); 6.52 (dd; *J*=7.81 , 1.22 Hz; H_5)]; 3.84 (H_{18}; dddd; *J*= 7.61, 6.92, 5.42, and 2.74 Hz); 3.71 ($H_{8(8')}$; dd, *J*=12.32, 2.74 Hz); 3.56 ($H_{17(17')}$; dd; *J*=15.01 and 7.63 Hz); 3.50-3.44 (m; $H_{8(8')}$ and $H_{17(17')}$, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 167.98 (C_{16}); 153.08(C_{10}); 141.12 (C_6), 135.15(C_{15}); and 115.02 (C_1); 127.70, 126.05, 125.47, 125.00, 122.67, 121.50, 118.54, and 115.29 (C_2, C_3, C_4, C_5, C_{11}, C_{12}, C_{13}, and C_{14}); 45.76 (CH_2, C_8); 38.46 (CH, C_{18}); 38.34 (CH_2, C_{17}). HRMS (ESI): $C_{16}H_{14}N_2NaS_2$, $[M+Na]^+$ calcd: 321.04961; found: 321.0496.

References

1- a) Y. Sugimoto, T. Tarumi, Q. E. Zhao, Y. Fujii , and C. Kamei, Methods Find Exp. Clin. Pharmacol. **1998**, 20, 457; Chem. Abstr. **1999**, 130, 75926; b) J. David, and E. J. Wager, Psychopharmacol. **1998**, 12, 283; Chem. Abstr. **1999**, 130, 119446; c) P. I. Williams, and M. Smith, Eur. J. Anaesthesiol. **1999**, 16, 683; Chem. Abstr. **1999**, 131, 332076; d) R. Fringuelli, L. Milanese, and F. Schiaffella, Mini Rev. Med. Chem. **2005**, 5, 1061-73; e) O. O. Ajani, Arch. Pharm. Chem. Life Sci. **2012**, 345, 841-851.

2- a) B. S. Rathore, and M. Kumar, Bioorganic & Medicinal Chemistry. **2006**, 14, 5678; b) V. V. Dabholkar, and R. P. Gavande, Rasayan J. Chem. **2010**, 3, 655; c) Chem. Abstr. **2011**, 154, 434836..

3- V. Balasubramaniyan, P. Balasubramaniyan, and A. S. Shaikh, Tetrahedron, **1986**, 42, 2731.

4- M. Avenati, and P. Vogel, Helv. Chim. Acta, **1982**, 65, 204.

5- CCDC 949457 contains the supplementary crystallographic data for compound **3**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

6- F. Eiden, and U. Grusdt, Arch. Pharm. (Weinheim, Germany), **1987**, 320 (10), 1020.

7- V. Facchinetti, R. Reis, R. B. Gomes, R. A. Vasconcelos. Mini Rev. Org. Chem, **2012**, 9, 44-53.