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Article

Synthesis of Dithiocarbamates by Markovnikov Addition Reaction in PEG and Their Application in Amidoalkylation of Naphthols and Indoles

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Synthesis of dithiocarbamates by the one-pot three-component Markovnikov addition reaction of an amine, carbon disulfide and an alkyl vinyl ether or *N*-vinylpyrrolidone is reported in polyethylene glycol (PEG) under a mild and green procedure with high yields and completely regiospecific. Also, the products were used as efficient starting materials for amidoalkylation of electron-rich arenes such as naphthols and indoles.

Keywords: dithiocarbamate, Markovnikov addition, alkyl vinyl ether, *N*-vinylpyrrolidone, polyethylene glycol

Introduction

Dithiocarbamates are the analogue of carbamates in which both oxygen atoms are replaced by sulfur atoms. The dithiocarbamate group is a valuable pharmacophore that induces various biological activity when incorporated into a particular structure.[1-4] Their biological potencies such as anti-histaminic, anti-bacterial, and anti-cancer are noteworthy.[5-7] They constitute a large family of herbicides, fungicides and pesticides in agriculture and several compounds of this category such as zineb, maneb, nabam, ziram and ferbam have been commercialized. Also, their applications as sulfur vulcanization agents in rubber manufacturing,[8] and radical chain transfer agents in the reversible addition-fragmentation chain-transfer (RAFT) polymerizations are extensively investigated.[9] Furthermore, they have been used as versatile synthons for the preparation of diversities of organic materials such as thioureas,[10] isothiocyanates,[11] 2-imino-1,3-dithiolanes,[12] cyanamides,[13] heterocyclic rings,[14] the protection of aldehydes,[15] amide bond formation,[16] and protection of the amino groups in peptide synthesis.[17] Also, dithiocarbamates are important ligands in metal complexes.[18]

The classical synthesis of dithiocarbamates involves the use of thiophosgene, a chlorothioformate and an isothiocyanate which suffer from many drawbacks such as long reaction time, harsh reaction conditions and use of an expensive and toxic reagent, base and solvent. Due to the wide applications of dithiocarbamates, several useful procedures for the synthesis of these compounds have been developed by our group and others, via the one-pot condensation of amines, carbon disulfide and electrophiles such as alkyl halides, epoxides, carbonyl compounds and α,β-unsaturated compounds.[19-23] Very recently, a deep eutectic solvent (DES) was used by Azizi and Gholibeglo[24] for synthesis of dithiocarbamates in high yields via a one-pot, three-component Michael addition of an amine and carbon disulfide to an activated olefin. Due to the aforementioned applications of dithiocarbamates, synthesis of these compounds with different substitution patterns by a convenient and safe method has become a field of increasing interest in recent years.

Solvents play a critical role in organic reactions for mixing the ingredients to allow molecular interactions. Performing organic reactions without using harmful organic solvents is now of great interest in green organic synthesis. For this purpose, attempts have been made toward the use of green mediums such as water, supercritical fluids, ionic liquids and fluorous based systems. Polyethylene glycol (PEG) has recently been considered as a novel, recyclable and eco-friendly solvent in synthetic chemistry for various organic transformations[25-29] with odd properties such as commercial availability, thermal stability, low volatility,

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and biodegradability and immiscibility with a number of organic solvents. Generally, PEG is an inexpensive, non-toxic, bio-compatible and completely non-halogenated solvent. The fast growth of published works about PEGs in medicinal areas reflects the importance of PEG polymers mainly related to their low toxicity.[30,31] This inspired us to concentrate on synthesis of the biologically active dithiocarbamates under catalyst-free conditions using PEG as green medium.

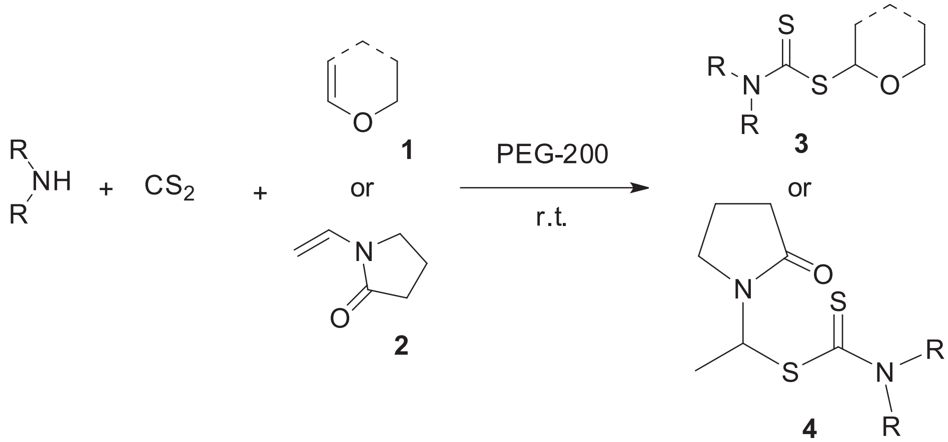
Results and Discussion

Previous reports by our group revealed that although high to excellent yields were obtained in the reaction of dithiocarbamates with alkyl vinyl ethers **1** in water,[22] for *N*-vinylpyrrolidine **2**, the reaction gave excellent yields under solvent-free conditions and no valuable yields were obtained in water.[23] To overcome this drawback, we focused our investigation to find an efficient reaction medium to be suitable for both systems. In continuation of our research allocated to the progress of green chemistry[32-36] and the chemistry of dithiocarbamates, herein we report a new and efficient protocol for synthesis of dithiocarbamates by Markovnikov addition reaction in PEG as a green and environmentally benign solvent at room temperature without using any catalyst as outlined in Scheme 1.

Initially, we examined the one-pot three-component reaction of pyrrolidine (5 mmol), CS_2 (6 mmol), and ethyl vinyl ether (6 mmol) in liquid polyethylene glycols such as PEG-200 and PEG-400. We found that excellent yield was obtained in PEG-200 (94%) in comparison to PEG-400 (65%). Also, mixing the starting materials at room temperature for 24 h was the best condition observed for this reaction.

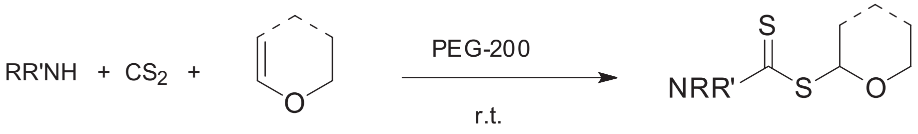
We then evaluated the scope and limitations of the protocol by employing a wide range of amines and electron-rich alkenes. The results are summarized in Tables 1 and 2. Various cyclic and acyclic alkyl vinyl ethers such as ethyl vinyl ether, ethyl propenyl ether and 2,3-dihydropyrane were examined with high to excellent yields (Table 1). *N*-Vinylpyrrolidone was also used in this transformation to afford excellent yields of products (Table 2). Primary aliphatic amines such as benzyl amine, allyl amine, cyclohexyl amine, furfuryl amine and butyl amine all gave excellent yields (entries 1-4, Table 1; and entries 1-4, Table 2). In addition, secondary amines such as pyrrolidine, piperidine, morpholine, azepane, diethyl amine, and diallyl amine reacted equally well in this protocol (entries 5-12, Table 1; entries 5-9, Table 2). Aromatic amines were not suitable starting materials for this transformation due to their low nucleophilic property toward carbon disulfide. The present method is experimentally simple and generates no byproducts. In addition, the reaction is regiospecific toward Markovnikov adducts. The PEG-200 can be simply recovered and reused in the reactions without a significant yield loss.

Having successfully synthesized Markovnikov adducts, we focused our attention on using the product **4** as suitable starting material for amidoalkylation of electron-rich arenes in the presence of $AlCl_3$ in refluxing chloroform (Scheme 2). The results are summarized in Table 3. Electron-rich arenes such as indoles and naphthols were used in this Mannich-type amidoalkylation reaction and moderate to good yields of products were obtained. *N*,*N*-Dialkylanilines, dimethoxybenzene, catechol, 2-methoxy naphthalene, pyrrole and thiophene were also examined for this reaction without any result. The Markovnikov products of alkyl vinyl ethers were not suitable starting materials for this transformation.



Scheme 1. A one-pot three-component synthesis of Markovnikov adducts.

Table 1. Markovnikov addition reaction of dithiocarbamates to vinyl ethers



3

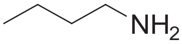
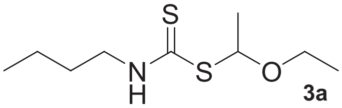
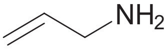
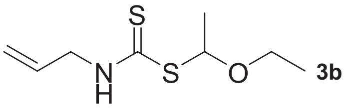
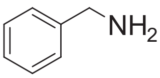
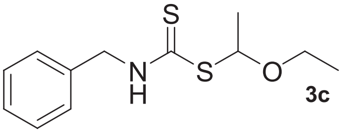
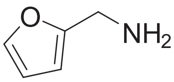
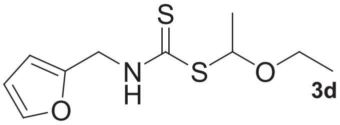
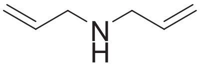
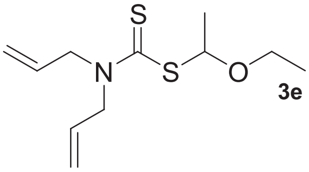
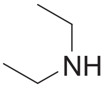
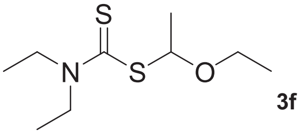
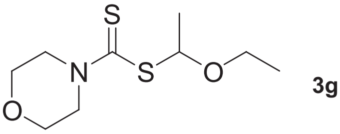
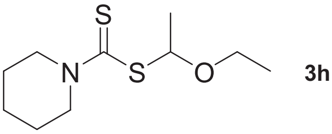
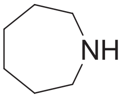
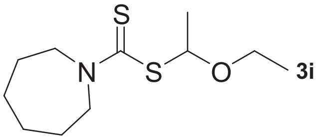
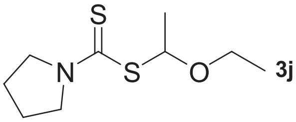
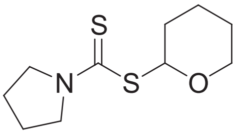
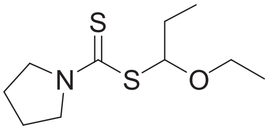
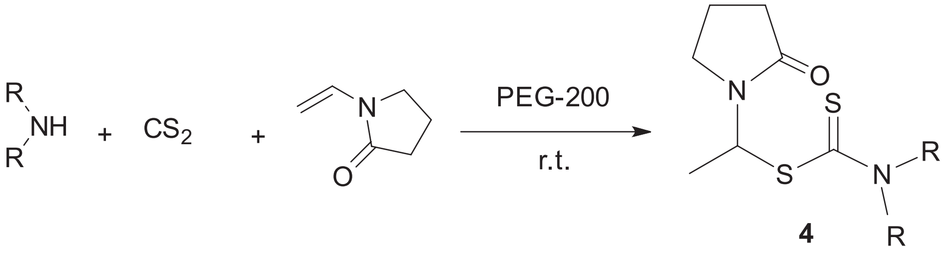
entry	Amine	Product	Yield^a / %
1		 **3a**	84
2		 **3b**	93
3		 **3c**	66
4		 **3d**	95
5		 **3e**	80
6		 **3f**	88
7		 **3g**	61
8		 **3h**	64
9		 **3i**	85
10		 **3j**	94

Table 1. Markovnikov addition reaction of dithiocarbamates to vinyl ethers (cont.)

entry	Amine	Product	Yield[a] / %
11		 **3k**	72
12		 **3l**	86

[a]Isolated yield.

Table 2. Markovnikov addition reaction of dithiocarbamates to *N*-vinylpyrrolidone



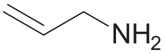
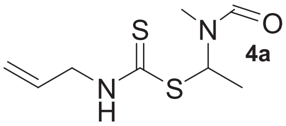
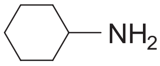
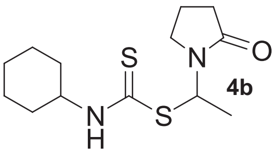
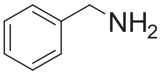
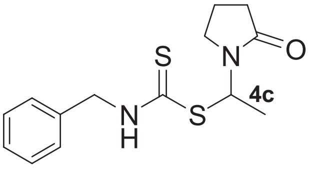
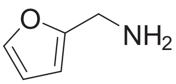
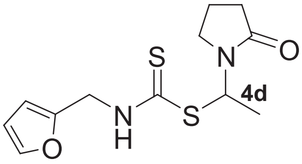
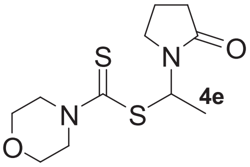
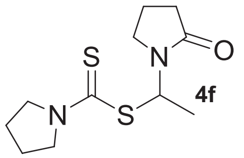
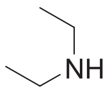
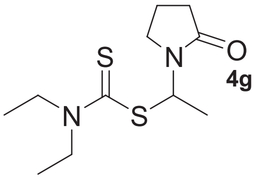
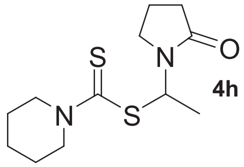
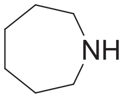
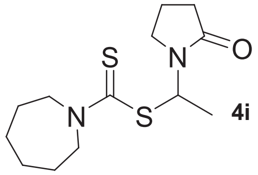
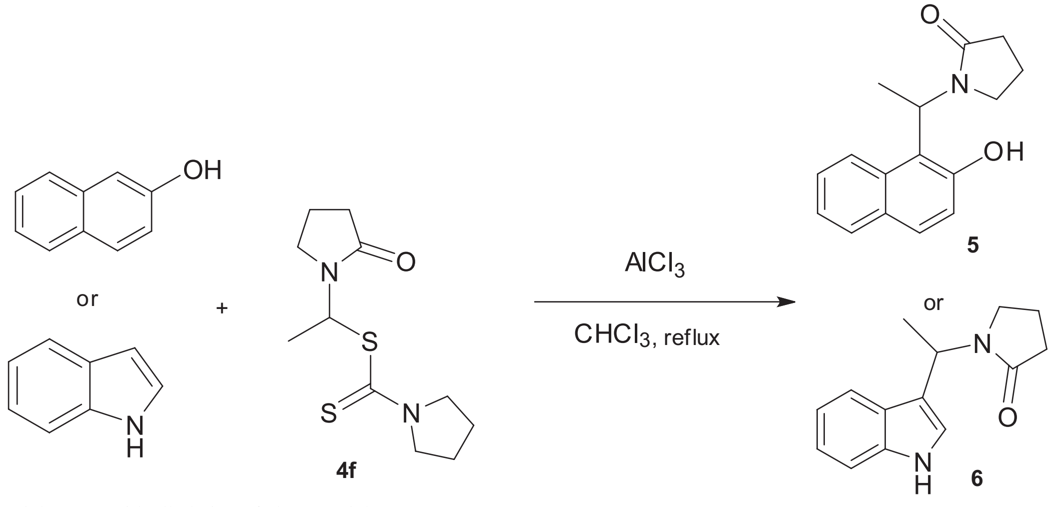
entry	Amine	Product	Yield[a] / %
1		 **4a**	93
2		 **4b**	80
3		 **4c**	66
4		 **4d**	95
5		 **4e**	61

Table 2. Markovnikov addition reaction of dithiocarbamates to *N*-vinylpyrrolidone (cont.)

entry	Amine	Product	Yield[a] / %
6		 **4f**	94
7		 **4g**	88
8		 **4h**	64
9		 **4i**	85

[a]Isolated yield.



Scheme 2. Mannich-type amidoalkylation of electron-rich arenes.

Conclusions

In summary, the PEG-200 has been employed as a novel, mild and highly efficient solvent for the one-pot three-component synthesis of dithiocarbamates via Markovnikov addition reaction in high to excellent yields. Regiospecificity for the Markovnikov adducts, clean reaction conditions, catalyst-free, and simple experimental procedures are the main advantages of this reaction. Also, the products were applied for the Friedel-Craft (Mannich) type amidoalkylation of electron-rich arenes such as indoles and naphthols.

Table 3. Mannich-type amidoalkylation of naphthols and indoles with dithiocarbamates prepared from Markovnikov reaction

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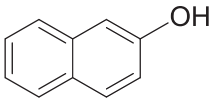
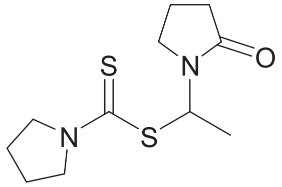
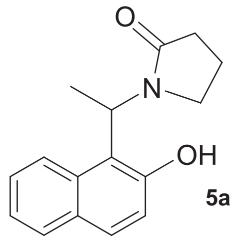
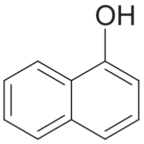
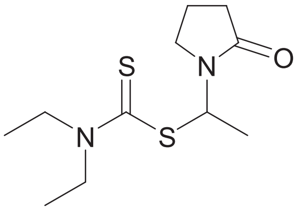
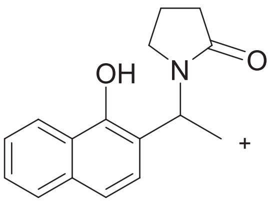
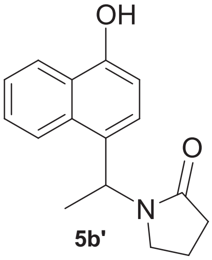
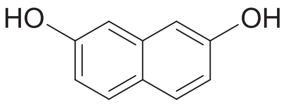
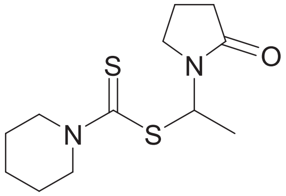
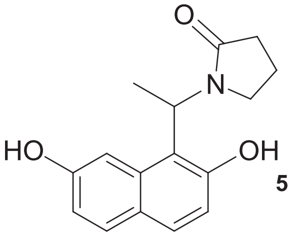
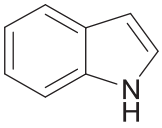
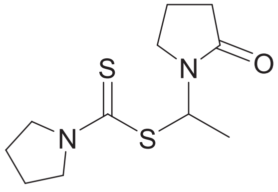
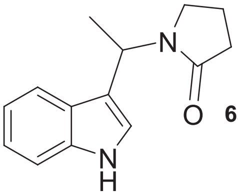
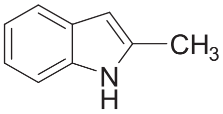
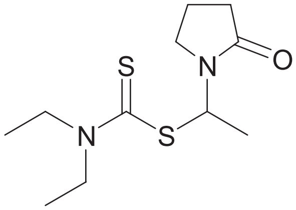
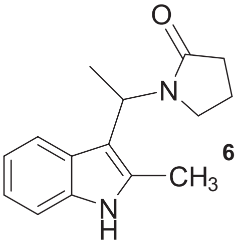
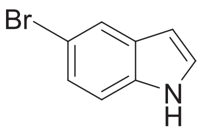
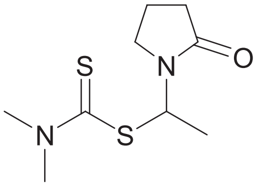
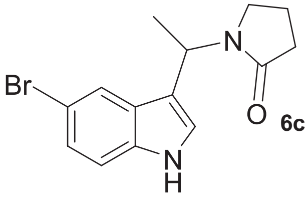
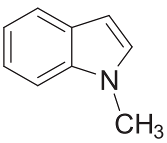
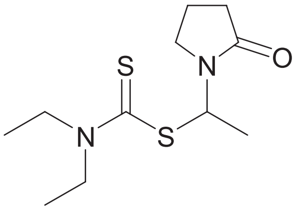
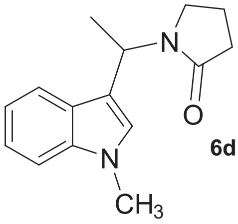
1			 **5a**	81
2			 **5b** +  **5b'**	62[b]
3			 **5c**	70
4			 **6a**	70
5			 **6b**	85
6			 **6c**	73
7			 **6d**	82

[a]Isolated yield; [b]total yields of regioisomers (5b:5b' = 2:1).

Experimental

All reactions were carried out in an atmosphere of air. All chemicals and solvents except water (tap water) were purchased from Merck or Fluka and used as received. All reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F254 (0.25 mm), and visualization was performed with UV. The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX 300-MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. Melting points were determined with a Branstead-Electrothermal 9200 apparatus and are uncorrected. Elemental analyses were conducted with a Perkin-Elmer 2004 (II) CHN analyzer.

General procedure for the synthesis of Markovnikov adducts **3a**-**l** and **4a**-**i**

To a mixture of an amine (5 mmol) and CS_2 (6 mmol) in PEG (10 mL) was added an electrophile (alkyl vinyl ether or *N*-vinyl pyrrolidine, 6 mmol). The reaction mixture was stirred vigorously at room temperature for 24 h. After completion of the reaction, H_2O (10 mL) was added and the product was extracted with EtOAc (2 × 20 mL) and combined organic layers were washed with H_2O and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the corresponding product with high purity without the need of column chromatography for purification. The PEG-200 can be recovered from the aqueous phase by passing the aqueous solution through activated charcoal and evaporation of water. All compounds were characterized on the basis of their spectroscopic data (^1H and ^{13}C NMR, CHN analysis) and by comparison with those reported in the literature.[22,23]

1-Ethoxyethyl azepane-1-carbodithioate (**3i**)

Viscous oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J* 7.0 Hz, CH_3), 1.42 (brs, 4H, $2CH_2$), 1.54 (d, 3H, *J* 6.3 Hz, CH_3), 1.69 (brs, 4H, $2CH_2$), 3.45 (m, 1H, CH_2O), 3.59 (m, 1H, CH_2O), 3.75 (t, 2H, *J* 6.0 Hz, CH_2N), 4.01 (m, 2H, CH_2N), 5.77 (q, 1H, *J* 6.2 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 22.9, 25.4, 25.9, 26.0, 27.2, 52.4, 54.4, 63.9, 90.1, 194.7; anal. calcd. for $C_{11}H_{21}NOS_2$: C, 53.40; H, 8.55; N, 5.66; found: C, 53.75; H, 8.71; N, 5.52.

1-Ethoxypropyl pyrrolidine-1-carbodithioate (**3l**)

Viscous oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* 7.3 Hz, CH_3), 1.03 (t, 3H, *J* 7.0 Hz, CH_3), 1.79-1.94 (m, 6H, $3CH_2$), 3.45-3.59 (m, 4H, CH_2N and CH_2O), 3.74 (t, 2H, *J* 6.9 Hz, CH_2N), 5.70 (t, 1H, *J* 6.1 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7, 14.4, 23.7, 26.1, 29.8, 50.2, 54.0, 64.0, 94.4, 191.6; anal. calcd. for $C_{10}H_{19}NOS_2$: C, 51.46; H, 8.21; N, 6.00; found: C, 51.23; H, 8.07; N, 6.12.

General procedure for amidoalkylation of electron-rich arenes **5a**-**c** and **6a**-**d**

In a 25 mL round bottom flask equipped with magnetic stirrer bar, an electron-rich arene (1 mmol), a dithiocarbamate **4** (1 mmol), chloroform (5 mL) and 10 mol% of $AlCl_3$ were added and the mixture was refluxed for 5-8 h. Progress of the reaction was monitored by TLC. After reaction completion, H_2O (10 mL) and $CHCl_3$ (10 mL) were added and the mixture was filtered to remove any undissolved materials. The filtrate was transferred to a decanter and the organic phase was separated. After treatment with Na_2SO_4, the solvent was evaporated to give the crude products. Purification was performed by recrystallization from ethyl acetate/petroleum.

1-(1-(2-Hydroxynaphthalen-1-yl)ethyl)pyrrolidin-2-one (**5a**)

Pale yellow solid; m.p. 198-200 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.67 (d, 3H, *J* 7.2 Hz, CH_3), 2.13-2.23 (m, 4H, $2CH_2$), 3.13 (m, 1H, CH_2N), 3.56 (m, 1H, CH_2N), 5.94 (q, 1H, *J* 7.2 Hz, CH), 7.14 (d, 1H, *J* 8.8 Hz, Ar–H), 7.25 (m, 1H, Ar–H), 7.40 (m, 1H, Ar–H), 7.68-7.76 (m, 2H, 2Ar–H), 8.10 (d, 1H, *J* 8.8 Hz, Ar–H), 9.8 (brs, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.3, 17.5, 30.6, 43.5, 44.4, 116.5, 119.1, 122.4, 126.5, 127.5, 128.3, 128.4, 129.2, 133.3, 154.5, 172.9; anal. calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49; found: C, 74.96; H, 6.71; N, 5.66.

1-(1-(1-Hydroxynaphthalen-2-yl)ethyl)pyrrolidin-2-one (**5b**)

Cream solid; m.p. 190-192 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.53 (d, 3H, *J* 6.8 Hz, CH_3), 1.58 (m, 1H, CH_2), 1.60 (m, 1H, CH_2), 2.16-2.39 (m, 2H, CH_2), 2.44 (m, 1H, CH_2N), 3.20 (m, 1H, CH_2N), 5.79 (q, 1H, *J* 6.8 Hz, CH), 6.85 (d, 1H, *J* 8.1 Hz, Ar–H), 7.37-7.50 (m, 3H, 3Ar–H), 7.89 (d, 1H, *J* 8.1 Hz, Ar–H), 8.15 (m, 1H, Ar–H), 10.18 (brs, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.3, 17.2, 30.8, 41.6, 44.5, 106.9, 122.6, 122.8, 124.4, 124.8 (2C), 125.5, 126.6, 132.3, 153.0, 172.6; anal. calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49; found: C, 75.66; H, 6.76; N, 5.47.

1-(1-(2,7-Dihydroxynaphthalen-8-yl)ethyl)pyrrolidin-2-one (**5c**)

Cream solid; m.p. 206-208 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.53 (d, 3H, *J* 7.1 Hz, CH_3), 1.63-2.23 (m, 4H, $2CH_2$), 3.15 (m, 1H, CH_2N), 3.55 (m, 1H, CH_2N), 5.73 (q, 1H, *J* 7.1 Hz, CH), 6.82 (dd, 1H, *J* 8.8, 1.8 Hz, Ar–H), 6.89 (d, 1H, *J* 8.8 Hz, Ar–H), 7.28 (s, 1H, Ar–H), 7.51 (d, 1H, *J* 8.9 Hz, Ar–H), 7.55 (d, 1H, *J* 8.7 Hz, Ar–H), 9.58 (s, 1H, OH), 9.70 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.4, 21.6, 30.7, 39.5, 44.6, 104.7, 114.7, 114.9, 115.6, 122.9, 128.9, 129.9, 135.1, 154.9, 156.0, 173.0; anal. calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16; found: C, 70.76; H, 6.25; N, 5.13.

1-(1-(1*H*-Indol-3-yl)ethyl)pyrrolidin-2-one (**6a**)

White solid; m.p. 164-167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, 3H, *J* 7.0 Hz, CH_3), 1.73-1.83 (m, 2H, CH_2), 2.41-2.88 (m, 2H, CH_2), 2.86 (m, 1H, CH_2N), 3.26 (m, 1H, CH_2N), 5.77 (q, 1H, *J* 7.0 Hz, CH), 7.08-7.22 (m, 3H, 2Ar–H and 1H, pyrrole), 7.36 (d, 1H, *J* 8.0 Hz, Ar–H), 7.62 (d, 1H, *J* 8.0 Hz, Ar–H), 8.31 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 17.7, 31.3, 42.2, 42.5, 111.0, 116.2, 119.5, 119.6, 121.1, 122.0, 126.4, 136.4, 174.2; anal. calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27; found: C, 74.01; H, 7.21; N, 12.61.

1-(1-(2-Methyl-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (**6b**)

White solid; m.p. 176-179 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74 (d, 3H, *J* 7.3 Hz, CH_3), 1.75-1.96 (m, 2H, CH_2), 2.34-2.43 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 3.17 (m, 1H, CH_2N), 3.57 (m, 1H, CH_2N), 5.76 (q, 1H, *J* 7.3 Hz, CH), 7.07-7.16 (m, 2H, 2Ar–H), 7.29 (dd, 1H, *J* 7.8, 2.0 Hz, Ar–H), 7.72 (d, 1H, *J* 7.8 Hz, Ar–H), 8.06 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 17.5, 17.7, 31.4, 43.4 (2C), 110.4, 110.6, 119.3, 119.5, 121.1, 127.9, 133.2, 135.0, 173.7; anal. calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56; found: C, 73.93; H, 7.65; N, 11.26.

1-(1-(5-Bromo-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (**6c**)

White solid; m.p. 155-157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, 3H, *J* 7.0 Hz, CH_3), 1.83-1.94 (m, 2H, CH_2), 2.44-2.49 (m, 2H, CH_2), 2.86 (m, 1H, CH_2N), 3.27 (m, 1H, CH_2N), 5.70 (q, 1H, *J* 7.0 Hz, CH), 7.15 (s, 1H, pyrrole ring), 7.24-7.31 (m, 2H, 2Ar–H), 7.74 (s, 1H, Ar–H), 8.70 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 17.7, 31.6, 42.2, 42.4, 112.7, 113.1, 115.7, 121.8, 123.3, 125.3, 128.0, 135.1, 174.3; anal. calcd. for $C_{14}H_{15}BrN_2O$: C, 54.74; H, 4.92; N, 9.12; found: C, 54.53; H, 4.83; N, 9.43.

1-(1-(1-Methyl-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (**6d**)

Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, 3H, *J* 7.0 Hz, CH_3), 1.80-1.93 (m, 2H, CH_2), 2.42-2.48 (m, 2H, CH_2), 2.92 (m, 1H, CH_2N), 3.30 (m, 1H, CH_2N), 3.79 (s, 3H, CH_3N), 5.78 (q, 1H, *J* 7.0 Hz, CH), 6.99 (s, 1H, pyrrole), 7.12 (m, 1H, Ar–H), 7.23-7.33 (m, 2H, 2Ar–H), 7.62 (dd, 1H, *J* 8.0, 0.7 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 17.7, 31.6, 32.7, 42.1, 42.4, 109.0, 114.6, 119.4, 119.7, 121.9, 126.6, 126.9, 137.1, 174.0; anal. calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56; found: C, 74.47; H, 7.65; N, 11.25.

Supplementary Information

Supplementary data (copies of ^{1}H and ^{13}C NMR spectra for unknown compounds) are available free of charge at http://jbcs.sbq.org.br as PDF file.

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