A SIMPLE AND EFFICIENT MICROWAVE MEDIATED SYNTHESIS OF NOVEL S- HETEROCYCLIC AMINOALKYLAMINO ETHNANE THIOLS

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Abstract: A very simple, efficient, microwave assisted synthesis for novel unsymmetrical thioethers with heterocyclic moieties under solvent free condition on solid support is described. This approach is convenient, straightforward, expeditious and environmentally benign.

Keywords: Microwave irradiation, Thioethers, Alumina, Heterocyclic, Solid support

Introduction

Thioethers containing heterocyclic moieties find wide application in pharmaceuticals and agrochemicals as drugs, herbicides, fungicides and insecticides due to their ability to serve both as reactive pharmacophores and biomimetics (1-2). Our interest was directed towards synthesis of S-heterocyclic thioethers with aminoalkyl backbone. Numerous synthetic procedures exists for the synthesis of thioethers, which centers on a common scheme of condensing metal alkyl or aryl thiolate with alkyl halide in the presence of either a base or a catalyst (3-11). Nevertheless, the synthetic scope of this reaction is often hampered by prolong reaction times, use of cumbersome bases, harsh reaction conditions, tedious work up, and the most serious drawback is incompatibility with other functional group in a multifunctional molecule. Furthermore, synthesis of thio ethers having amine backbone is often more tedious with aforesaid approach as the highly reactive amine functionality causes interference in synthetic transformation (12). Poor selectivity of such reactions, usually necessitates protection of the amine functionalities to avoid formation of undesired products (13). Protection-deprotection sequence in turn make the method more tedious and yields obtained are also poor.

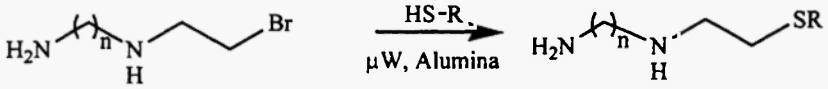
We were interested in developing a method which will enable us to prepare our target compounds through a straightforward simple and efficient approach. Organic reactions on solid supported reagents coupled with microwave; offer a powerful method for many organic reactions, due to their greater selectivity, enhanced reaction rate, cleaner reaction products and operational simplicity (14). With the best of our understanding no such method is available for the synthesis of S-heterocyclic thioethers with aminoalkyl backbone. Hence, we explored the possibility of the synthesis of our target compound by this approach and herein, we present a very simple and efficient microwave assisted, solvent free synthesis of S-heterocyclic thioethers with aminoalkyl backbone.

Result and Discussion

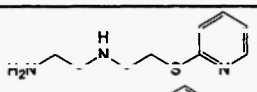
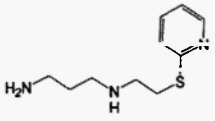
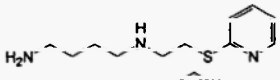
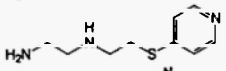
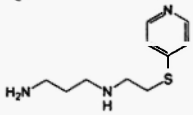
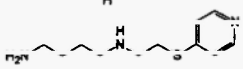
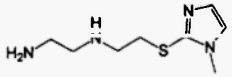
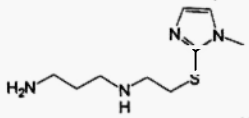
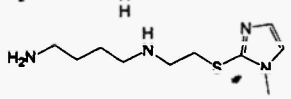
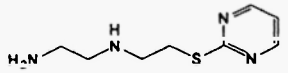
Due to the availability of synthetic precursors, aminoalkylamino ethyl bromides were selected as key intermediate for all the compounds. We preferred taking these bromides in the form of dihydrobromide salt as these salts were stable to atmospheric oxygen, nonvolatile and non odorous. The added advantage of the taking amines in

the form of their dihydrobromide salt is that the amino groups being protected by protonation, do not interfere in the reaction. Interestingly, we also observed that in the presence of a little moisture these salts melt safely below their decomposition temperatures; this eliminates the need of an external solvent for carrying out the reaction. Furthermore, we reasoned that basic nitrogen containing heterocyclic mercaptan can themselves act as base for catalyzing the reaction. In light of above observations/rationals we investigated the synthesis of our target compounds with microwave irriadiation under solvent less condition.

Table 1: Synthesis of S-2-(ω-aminoalkylamino) ethyl heterocyclic thioethers[a] $NH_2(CH_2)_nNHCH_2CH_2SR$



n = 2, 3, 4 R = 2-pyridyl, 4-pyridyl, 2-imidazolyl, 2-pyrimidyl

Entry	n	R	Product[a]	Yield (%)
1.	2		1a	 85
2.	3	„	1b	 87
3.	4	„	1c	 82
4.	2		2a	 81
5.	3	„	2b	 80
6.	4	„	2c	 81
7.	2		3a	 89
8.	3	„	3b	 86
9.	4	„	3c	 83
10.	3		4a	 84

[a]All the compounds were isolated as trihydrochloride salts (15); spectral data (^{1}H-NMR and ESI Mass spectra) were found to be satisfactory

For this work we used the simple domestic microwave oven (Samsung CE2977N) operating at 2450 MHz. First, we attempted the reaction using a homogeneous mixture of dihydrobromide salt of aminoalkyl bromide and mercaptan with few drops of water in a conical flask and subjecting it to microwave irradiation. Though the reaction occurred in the desired way, but, satisfactory results could not be obtained as contents were getting charred before completion of the reaction, because of hot spot formation. This problem was overcome by dispersing the reagents uniformly on an inert solid support (alumina) followed by microwave irradiation. The influence of the solid support seems to be in aiding the reaction by uniformly distributing the reactants. This allows better penetration of microwaves, preventing localised heating.

In a typical synthetic reaction 0.025 mol of dihydorbromide salt of aminoalkylamino ethyl bromide and 0.025 mol of the desired heterocyclic mercaptan were dissolved in minimum quantity of methanol and 10 gm. of inert alumina was added to it. The contents were mixed on a cyclomixer to form a homogeneous paste. Methanol was removed under vacuum and to the solid residue 1-2 drops of water was added to facilitate the absorption of microwave and again thoroughly mixed. Irradiation was performed by placing the mixture in a conical flask at 180W for different time intervals (60-100 sec.). The microwave exposure was intermittent with 15 second break. Instantaneous reaction takes place with simultaneous formation of thioethers. The reaction was monitored by TLC. On completion of the reaction, the residue was washed with methanol and filtered. Acetone was added to the filtrate and compound was obtained as pale yellow solid in the form of trihydrobromide salt (Table 1.)

Spectral Data for the compounds

N^1-[2-(Pyridin-2-ylsulfanyl)-ethyl]-ethane-1, 2-diamine.dihydrochloride salt 1a
IR (KBr cm^{-1}): 2971, 2890, 2708, 1603, 1514, 1479, 1106, 828, 780. ^1H NMR (CD_3OD): (δ ppm) 8.52 (m, 1H), 8.31 (m, 1H), 7.52 (d, 1 H), 7.45 (m, 1H), 3.60 (t, 2H), 3.41 (t, 2H), 3.35 (m, 2H), 3.28 (m, 2H) MS ESI (m/z): 198 $(M+H)^+$.
N^1-[2-(Pyridin-2-ylsulfanyl)-ethyl]-propane-1, 3-diamine.dihydrochloride salt 1b
IR (KBr cm^{-1}): 2955, 2890, 2749, 1605, 1529, 1444, 1444, 1384, 780. ^1H NMR (CD_3OD): (δ ppm) 8.53 (m, 1H), 7.89 (m, 1 H), 7.60(d, 1H), 7.35 (m, 1H), 3.57 (t, 2H), 3.42 (t, 2H), 3.19 (t, 2H), 3.07 (t, 2H), 2.11 (m, 2H) MS ESI (m/z): 212 $(M+H)^+$.
N^1-[2-(Pyridin-2-ylsulfanyl)-ethyl]-butane-1, 4-diamine. dihydrochloride salt 1c
IR (KBr cm^{-1}): 2996, 2965, 2762, 1604, 1445, 1388, 780. ^1H NMR (CD_3OD) :(δ ppm) 8.54 (m, 1H), 7.87 (m, 1 H), 7.60(d, 1H), 7.34 (m, 1H), 3.57 (t, 2H), 3.43 (t, 2H), 3.20 (t, 2H), 3.06 (t, 2H), 2.09 (m, 4H) MS ESI (m/z): 226 $(M+H)^+$
N^1-[2-(Pyridin-4-ylsulfanyl)-ethyl]-ethane-1, 2-diamine.dihydrochloride salt 2a
IR (KBr cm^{-1}): 2928, 2749, 1623, 1540, 1479, 1218, 1106, 828, 780. ^1H NMR (CD_3OD): (δ ppm) 8.56 (d, 2H), 8.04 (d, 2H), 3.58 (t, 2H), 3.41 (t, 2H), 3.35 (m, 2H), 3.28 (m, 2H) MS ESI (m/z): 198 $(M+H)^+$
N^1-[2-(Pyridin-4-ylsulfanyl)-ethyl]-propane-1, 3-diamine.dihydrochloride salt 2b
IR (KBr cm^{-1}): 2982, 2927, 2756, 2722, 1620, 1586, 1468, 1170, 916, 785. ^1H NMR (CD_3OD): (δ ppm) 8.55 (d, 2H), 8.05 (d, 2H), 3.67 (t, 2H), 3.42 (t, 2H), 3.15 (t, 2H), 2.99 (t, 2H), 1.83 (m, 2H). MS ESI (m/z): 212 $(M+H)^+$.
N^1-[2-(Pyridin-4-ylsulfanyl)-ethyl]-butane-1, 4-diamine.dihydrochloride salt 2c
IR (KBr cm^{-1}): 2944, 2916, 2734, 1625, 1606, 1488, 1104, 818, 778. ^1H NMR (CD_3OD): (δ ppm) 8.56 (d, 2H), 8.04 (d, 2H), 3.68 (t, 2H), 3.42 (t, 2H), 3.14 (t, 2H), 2.99 (t, 2H), 1.81 (m, 2H) . MS ESI (m/z): 226 $(M+H)^+$

N^1-[2-(1-Methyl-1H-imidazol-2-ylsulfanyl)-ethyl]-ethane-1,2-diamine.dihydrochloride salt 3a

IR (KBr, cm^{-1}): 2961, 1578, 1024, 920, 756. ^1H NMR (CD_3OD): (δ ppm) 7.76 (d, 1H), 7.65 (d, 1H), 3.95 (s, 3H), 3.46 (t, 2H), 3.33, (t, 2H), 3.18 (t, 2H), 3.09 (t, 2H). MS ESI (m/z): 201 $(M+H)^+$

N^1-[2-(1-Methyl-1H-imidazol-2-ylsulfanyl)-ethyl]-propane-1,3-diamine.dihydrochloride salt 3b

IR (KBr, cm^{-1}): 2960, 2924, 1578, 1432, 748.^1H NMR (CD_3OD): (δ ppm) 7.73 (d, 1H), 7.67 (d, 1H), 3.98 (s, 3H), 3.47 (t, 2H), 3.34, (t, 2H), 3.18 (t, 2H), 3.08 (t, 2H), 2.12 (m, 2H). MS ESI: (m/z) 215 $(M+H)^+$

N^1-[2-(1-Methyl-1H-imidazol-2-ylsulfanyl)-ethyl]-butane-1,4-diamine.dihydrochloride salt 3c

IR (KBr, cm^{-1}): 2956, 1575, 1459, 779 ^1H NMR (CD_3OD) :(δ ppm) 7.74 (d, 1H), 7.66 (d, 1H), 3.98 (s, 3H), 3.48 (t, 2H), 3.31 (t, 2H), 3.18 (t, 2H), 3.08 (t, 2H), 2.12 (m, 4H). MS ESI: (m/z) 229 $(M+H)^+$

N^1-[2-(Pyrimidin-2-ylsulfanyl)-ethyl]-ethane-1, 2-diamine.dihydrochloride salt 4a

IR (KBr, cm^{-1}): 2959, 2923, 1564, 1465, 770 ^1H NMR (CD_3OD) :(δ ppm) 8.62 (d, 2H), 7.30 (t, 1H), 3.51 (m, 2H), 3.44 (m, 2H), 3.19 (t, 2H), 3.07 (t, 2H), 2.12 (m, 2H) MS ESI: (m/z) 199 $(M+H)^+$

Conclusion

In summary, we have developed a very convenient, simple, expeditious and solvent-less microwave assisted method for the preparation of novel Aminoalkyl S-heterocyclic thioethers.

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15. For pharmacological evaluation, we required the compounds in the form of hydrochloride salts. For this the pale yellow solid obtained was treated with conc. sodium hydroxide solution (containing 3.1 mol NaOH) and contents were extracted with chloroform. Solvent removal afforded a pale yellow liquid which was diluted with anhydrous ethanol and converted to white crystalline hydrochloride salt with gaseous HCl. Further purification if required was achieved by dissolving the compound in methanol and precipitating it with acetone.

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