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MICROWAVE-ASSISTED DEHYDROSULFURIZATION: AN EFFICIENT, SOLVENT-FREE SYNTHESIS OF 5-(1-ADAMANTYL)-2-ARYLAMINO-1,2,4-TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLES

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Abstract – A fast and efficient microwave-assisted synthesis of 2-arylamino-5-(1-adamantyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles is described. The reaction of 3-(1-adamantyl)-5-mercapto-1,2,4-triazole (**2**) with arylisothiocyanates in DMF at room temperature yielded the corresponding *N,N'*-disubstituted thioureas (**3a-e**) in high yields. Compounds (**3a-e**) were desulfurized *via* microwave irradiation for 5 min to yield the corresponding 5-(1-adamantyl)-2-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (**4a-e**). Compounds (**4a-e**) were also prepared in good yields *via* microwave irradiation of a mixture of (**2**) and the corresponding arylisothiocyanates for 8 minutes. Attempted preparation of the aliphatic analogues (**6a-e**) *via* microwave irradiation was unsuccessful, they were obtained in poor yields *via* prolonged heating of compound (**2**) with the corresponding aliphatic isothiocyanate in DMF. Compounds (**6a-e**) were independently obtained in good yields *via* the reaction of (**2**) with cyanogen bromide to yield the 2-amino analogue (**7**) that was subsequently reacted with the corresponding aliphatic halide.

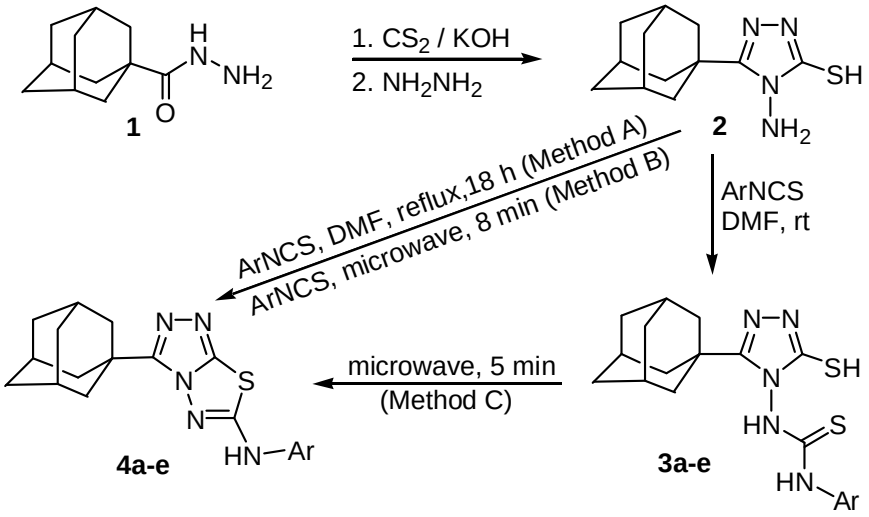
INTRODUCTION

Several adamantane derivatives have long been known for their antiviral activity against Influenza A[1-6] and HIV viruses.[7-10] In addition, a number of adamantane derivatives were also associated with central nervous,[11-13] antimicrobial,[14-19] and anti-inflammatory activities.[18-22] 1,2,4-Triazolo[3,4-*b*][1,3,4]-thiadiazole derivatives were also reported to possess significant antibacterial and antifungal activities.[23-26] In continuation to our interest in the chemical and biological properties of adamantane derivatives,[10,18,19,22,27,28] and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles,[28-31] we report herein the synthesis of

new series of 5-(1-adamantyl)-2-substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles as potential antimicrobial agents.

RESULTS AND DISCUSSION

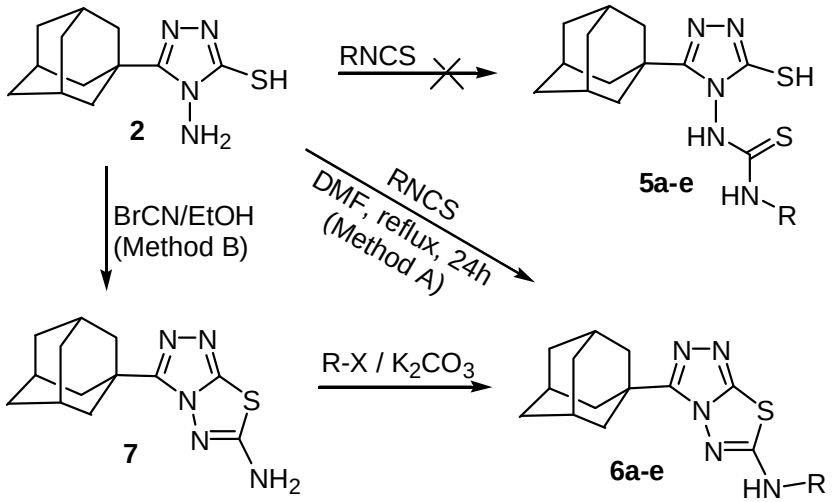
Several methods were reported for the synthesis of 2,5-disubstituted-1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazoles utilizing either 1,3,4-thiadiazoles or 1,2,4-triazoles as starting materials. The use of 1,3,4-thiadiazoles as precursors for 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles utilizes mainly 2-hydrazino-1,3,4-thiadiazoles as starting materials through reaction with alkyl orthoformate,[32] cyanogen bromide or carbon disulphide.[33] The disadvantage of these methods are the numerous steps for the preparation of the starting materials and the poor overall yields. 4-Amino-5-mercapto-3-substituted-1,2,4-triazoles are excellent precursors for 2,5-disubstituted-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. The reactions utilizing these precursors include dehydrative ring closure of the 4-acylamino derivatives,[32] heating with carboxylic acids and phosphorus oxychloride,[25,26,30,34] heating with arylnitriles in the presence of aluminium chloride,[35] and oxidative cyclization of the 4-arylideneamino derivatives.[29] In addition, the reaction of 4-amino-5-mercapto-1,2,4-triazoles with cyanogen bromide or carbon disulfide afforded good yields of the corresponding 2-amino or mercapto-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles, respectively.[26,36,37] In the last decade, microwave irradiation was introduced as a useful alternative to the traditional heating for the synthesis of several heterocyclic derivatives including 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives.[38,39] The reaction of 4-amino-5-mercapto-3-substituted-1,2,4-triazoles with arylisothiocyanates was reported to yield the cyclic 2-arylamino-1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazole[40] or the acyclic *N*,*N*′-disubstituted thiourea derivatives,[24,26,40] depending on the reaction conditions. Thus, 3-(1-adamantyl)-4-amino-5-mercapto-1,2,4-triazoles (**2**), required as starting material, was prepared *via* the reaction of adamantane-1-carbohydrazide (**1**) with carbon disulfide and potassium hydroxide, followed by reaction with hydrazine.[28] Trials to react compound (**2**) with arylisothiocyanates in EtOH *via* prolonged heating up to 24 h were unsuccessful, and the reactants were separated unchanged. Meanwhile, carrying out the reaction in DMF at room temperature for 24 h yielded the corresponding *N*,*N*′-disubstituted thiourea derivatives (**3a-e**) in excellent yields (89-95%). On the other hand, prolonged heating of (**2**) with arylisothiocyanates yielded the cyclic dehydrosulfurized products (**4a-e**) in 51-63% yields (Method A). Compounds (**3a-e**) were also dehydrosulfurized to the corresponding (**4a-e**) derivatives by heating in DMF for 18 h. A better result was obtained *via* microwave irradiation of compounds (**3a-e**) for 5 min and the products (**4a-e**) were obtained in 92-95% yields (Method C). The reaction of **2** with arylisothiocyanate under microwave irradiation for 8 min in the absence of solvent (Method B) was found to be superior to method A and the products were easily obtained in high yields (82-89%) in very short time (Scheme 1, Table 1).



Scheme 1

Trials to react compound (**2**) with methyl, ethyl, allyl, *n*-butyl, or benzyl isothiocyanate in DMF at room temperature to get the corresponding *N*,*N*′-disubstituted thiourea derivatives (**5a-e**) were unsuccessful, whereas, carrying out the reaction under reflux for 24 h yielded the corresponding 5-(1-adamantyl)-2-substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole (**6a-e**) in 34-42% yields (Method A). In contrary to the reaction with arylisothiocyanates, microwave irradiation of (**2**) with the aliphatic isothiocyanates for 10 min failed to yield compounds (**6a-e**). Increasing the irradiation time or intensity resulted in carbonization of the reactants. Compounds (**6a-e**) were prepared in good overall yields through reaction of (**2**) with cyanogen bromide in EtOH to yield 5-(1-adamantyl)-2-amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole (**7**), which was subsequently reacted with the appropriate halide in ethanol in the presence of potassium carbonate to afford good yields (82-92%) of the corresponding 5-(1-adamantyl)-2-substituted amino-1,2,4-triazolo[3,4-*b*][1,3, 4]thiadiazole (**6a-e**) (Scheme 2, Table 1). The structures of the newly synthesized compounds were confirmed by elemental analyses, ^{1}H NMR, ^{13}C NMR, and mass spectra.

Compounds (**3a-e**, **4a-e**, **6a-e** and **7**) were tested for their *in vitro* antimicrobial activity against a panel of standard pathogenic strains of the Institute of Fermentation of Osaka (IFO), namely the Gram-positive bacteria *Staphylococcus aureus* IFO 3060, *Bacillus subtilis* IFO 3007 and *Micrococcus luteus* IFO 3232, the Gram-negative bacteria *Escherichia coli* IFO 3301 and *Pseudomonas aeuroginosa* IFO 3448, and the yeast-like pathogenic fungus *Candida albicans* IFO 0583. The screening was carried out using the agar disc-diffusion method and determination of the minimal inhibitory concentrations (MIC).[41] The results of the antimicrobial testing revealed that compounds (**3a-e** and **7**) are highly active against the tested Gram-positive bacteria, while compounds (**4a-e** and **6a-e**) were weakly active or inactive. Meanwhile, the tested compounds were found completely inactive against the tested Gram-negative bacteria and *Candida albicans*.



Scheme 2

EXPERIMENTAL

Melting points (°C, uncorrected) were determined using a Gallenkamp melting point apparatus. Microwave irradiation was performed using an Akai MW-GB092MP (800 W) unmodified domestic microwave oven operated at 2450 MHz. NMR spectra were obtained on a Bruker AC 500 Ultra Shield NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, the chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane (TMS). Electron impact mass spectra were recorded on a Shimadzu GC–MS-QP 5000 instrument at 70 eV.

***N*-[3-(1-Adamantyl)-5-mercapto-1,2,4-triazol-4-yl]-*N'*-arylthioureas (3a-e):** The appropriate aryl-isothiocyanate (2 mmol) was added to a solution of 3-(1-adamantyl)-5-mercapto-1,2,4-triazole (**2**) (0.5 g, 2 mmol) in dry DMF (8 mL), and the solution was stirred at rt for 24 h. Water (20 mL) was then added and the mixture was stirred for 20 min. The separated precipitate was filtered, washed with water and crystallized from EtOH.

3a: ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, adamantane-H), 2.07 (s, 9H, adamantane-H), 7.31-7.52 (m, 5H, Ar-H), 9.85 (s, 1H, NH), 10.02 (s, 1H, NH), 13.48 (s, 1H, SH). ^{13}C NMR: δ 27.85, 34.82, 36.58, 38.40 (adamantane-C), 125.41, 126.86, 128.20, 132.55 (Ar-C), 139.53 (triazole C-5), 157.32 (triazole C-3), 167.82 (C=S). MS, *m/z* (Rel. Int.): 385 (M^+, 1), 351 (3), 268 (11), 234 (13), 209 (23), 167 (29), 136 (34), 135 (88), 109 (16), 93 (44), 91 (17), 77 (100).

3b: ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 6H, adamantane-H), 2.02 (s, 3H, adamantane-H), 2.06 (s, 6H, adamantane-H), 6.81 (s, 1H, Ar-H), 7.35-7.39 (m. 3H, Ar-H), 9.77 (s, 1H, NH), 10.04 (s, 1H, NH), 13.47 (s, 1H, SH). ^{13}C NMR: δ 27.80, 34.81, 36.52, 38.37 (adamantane-C), 111.61, 113.10, 118. 65, 130.11, 138.32, 161.09 (Ar-C), 141.50 (triazole C-5), 163.02 (triazole C-3), 167.74 (C=S). MS, *m/z* (Rel. Int.):

369 (M^+ -H_2S, 2), 234 (36), 218 (11), 169 (8), 135 (65), 95 (77), 41 (100).

3c: ^{1}H NMR (DMSO-d_6): δ 1.70 (s, 6H, adamantane-H), 1.96-2.08 (m, 9H, adamantane-H), 7.16 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.50 (d, 2H, *J* = 8.1 Hz, Ar-H), 9.82 (s, 1H, NH), 10.66 (s, 1H, NH), 13.50 (s, 1H, SH). ^{13}C NMR: δ 27.88, 34.65, 36.59, 38.44 (adamantane-C), 114.50, 126.17, 134.52, 157.22 (Ar-C), 136.08 (triazole C-5), 161.90 (triazole C-3), 167.90 (C=S). MS, *m/z* (Rel. Int.): 403 (M^+, 1), 369 (3), 234 (42), 135 (81), 95 (75), 41 (100).

3d: ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, adamantane-H), 2.06 (s, 9H, adamantane-H), 7.37 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.55 (d, 2H, *J* = 8.0 Hz, Ar-H), 9.98 (s, 1H, NH), 10.72 (s, 1H, NH), 13.49 (s, 1H, SH). ^{13}C NMR: δ 27.86, 34.85, 36.88, 38.48 (adamantane-C), 125.52, 128.54, 131.35, 137.98 (Ar-C), 142.60 (triazole C-5), 157.23 (triazole C-3), 167.81 (C=S). MS, *m/z* (Rel. Int.): 419 (M^+, 1), 385 (3), 234 (43), 135 (44), 126 (11), 41 (100).

3e: ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 6H, adamantane-H), 2.02 (s, 3H, adamantane-H), 2.07 (s, 6H, adamantane-H), 7.40 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.64 (d, 2H, *J* = 8.5 Hz, Ar-H), 9.82 (s, 1H, NH), 10.81 (s, 1H, NH), 13.64 (s, 1H, SH). ^{13}C NMR: δ 27.81, 34.81, 36.53, 38.38 (adamantane-C), 121.07, 126.18, 128.43, 133.28 (Ar-C), 139.24 (triazole C-5), 157.08 (triazole C-3), 167.73 (C=S). MS, *m/z* (Rel. Int.): 465 (M^+ +2, 1), 463 (M^+, 1), 431 (2), 429 (3), 234 (100), 159 (19), 157 (22), 135 (68), 41 (78).

5-(1-Adamantyl)-2-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (4a-c): ***Method A:*** The appropriate arylisothiocyanate (2 mmol) was added to a solution of 3-(1-adamantyl)-5-mercapto-1,2,4-triazole (**2**) (500 mg, 2 mmol) in dry DMF (8 mL) and the solution was heated under reflux for 18 h. On cooling, the mixture was poured onto cold water (30 mL) and the separated precipitate was filtered, washed with water and crystallized to yield compounds (**4a-e**) in 51-63% yields. ***Method B:*** Equimolar amounts (2 mmol) of compound (**2**) and the appropriate arylisothiocyanate were thoroughly mixed and placed in 50 mL open round bottom flask, and the mixture was irradiated in the microwave oven for 8 min at 454 W (58%). On cooling, $CHCl_3$ (10 mL) was added and the reaction mixture was stirred for 5 min, then filtered and the filtrate was evaporated *in vacuo*. The crude products were crystallized from EtOH to yield compounds (**4a-e**) in 82-89% yields. ***Method C:*** The appropriate *N*,*N*′-disubstituted thiourea (**3a-c**) (2 mmol) was irradiated in the microwave oven for 5 min at 454 W (58%) and treated as described in method B to yield compound (**4a-c**) in 92-95% yields.

4a: ^{1}H NMR ($CDCl_3$): δ 1.79 (s, 6H, adamantane-H), 2.10 (s, 3H, adamantane-H), 2.15 (s, 6H, adamantane-H), 7.06-7.58 (m, 6H, Ar-H and NH). ^{13}C NMR: δ 27.85, 34.33, 36.80, 39.15 (adamantane-C), 118.50, 124.06, 129.82, 139.92 (Ar-C), 149.69 (C-8), 153.14 (C-5), 180.05 (C-2). MS, *m/z* (Rel. Int.): 351 (M^+, 4), 268 (27), 234 (26), 150 (30), 135 (23), 118 (17), 104 (34), 91 (38), 77 (100).

Table 1: Crystallization solvents, melting points, yield percentages, and microanalytical data of compounds (**3a-e**, **4a-e** and **6a-g**).

Comp. No.	Ar / R	Cryst. Solvent	Mp (°C)	Yield (%)	Analysis: % Calcd. (Found)			
					C	H	N	S
3a	C_6H_5	EtOH	231-3	92	59.19 (58.87)	6.01 (6.03)	18.16 (18.05)	16.63 (16.55)
3b	3-FC_6H_4	EtOH	252-4	89	56.55 (56.33)	5.50 (5.53)	17.35 (17.29)	15.89 (15.81)
3c	4-FC_6H_4	EtOH	207-9	95	56.55 (56.34)	5.50 (5.47)	17.35 (17.28)	15.89 (15.77)
3d	4-ClC_6H_4	EtOH	242-4	95	54.33 (54.01)	5.28 (5.31)	16.67 (16.58)	15.27 (15.19)
3e	4-BrC_6H_4	EtOH	246-8	94	49.13 (48.91)	4.77 (4.81)	15.08 (15.01)	13.81 (13.76)
4a	C_6H_5	EtOH/H_2O	> 300	56 (82)[a]	64.93 (64.66)	6.02 (5.97)	19.93 (19.77)	9.12 (9.16)
4b	3-FC_6H_4	EtOH/H_2O	> 300	55 (86)[a]	61.77 (61.82)	5.46 (5.52)	18.96 (18.88)	8.68 (8.72)
4c	4-FC_6H_4	EtOH/H_2O	> 300	51 (88)[a]	61.77 (62.01)	5.46 (5.48)	18.96 (18.94)	8.68 (8.70)
4d	4-ClC_6H_4	MeOH	> 300	56 (89)[a]	59.13 (58.87)	5.22 (5.33)	18.15 (18.07)	8.31 (8.26)
4e	4-BrC_6H_4	EtOH/H_2O	302-4	63 (85)[a]	53.03 (52.88)	4.68 (4.71)	16.27 (16.11)	7.45 (7.36)
6a	CH_3	MeOH	245-7	34 (88)[b]	58.10 (57.86)	6.62 (6.65)	24.20 (24.05)	11.08 (11.13)
6b	C_2H_5	MeOH	252-4	37 (89)[b]	59.38 (59.30)	6.98 (7.01)	23.08 (22.95)	10.57 (10.53)
6c	CH_2=$CHCH_2$	EtOH/H_2O	280-2	39 (82)[b]	60.92 (60.71)	6.71 (6.75)	22.20 (22.09)	10.17 (10.21)
6d	C_4H_9(*n*)	MeOH	269-71	42 (85)[b]	61.60 (61.42)	7.60 (7.64)	21.13 (21.06)	9.67 (9.71)
6e	$C_6H_5CH_2$	MeOH	271-3	41 (92)[b]	65.72 (65.45)	6.34 (6.37)	19.16 (19.24)	8.77 (8.74)

[a] The figures shown in parentheses represent the yields obtained *via* microwave irradiation (Method B).
[b] The figures shown in parentheses represent the yields obtained *via* the reaction of compound **(7)** with the aliphatic halides

4b: ^{1}H NMR ($CDCl_3$): δ 1.72 (s, 6H, adamantane-H), 2.01 (s, 3H, adamantane-H), 2.08 (s, 6H, adamantane-H), 6.85 (s, 1H, Ar-H), 7.23 (s, 1H, NH), 7.33-7.72 (m, 3H, Ar-H). ^{13}C NMR: δ 27.80, 34.18, 36.53, 38.38 (adamantane-C), 106.06, 110.62, 113.29, 130.90, 151.02, 163.25 (Ar-C), 149.90 (C-8), 157.08 (C-5), 179.82 (C-2). MS, *m/z* (Rel. Int.): 369 (M^+, 5), 350 (6), 234 (14), 191 (36), 176 (28), 160 (100) 135 (62), 111 (12), 104 (60).

4c: ^{1}H NMR ($CDCl_3$): δ 1.72 (s, 6H, adamantane-H), 2.09 (s, 3H, adamantane-H), 2.14 (s, 6H, adamantane-H), 7.26-7.30 (m, 2H, Ar-H), 7.56-7.60 (m, 3H, Ar-H and NH). ^{13}C NMR: δ 27.40, 34.32, 35.99, 39.0 (adamantane-C), 115.63, 120.28, 136.32, 153.16 (Ar-C), 149.68 (C-8), 159.85 (C-5), 177.86 (C-2). MS, *m/z* (Rel. Int.): 369 (M^+, 8), 350 (3), 234 (11), 191 (47), 176 (15), 135 (68), 109 (100), 104 (33).

4d: ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 6H, adamantane-H), 1.98 (s, 3H, adamantane-H), 2.11 (s, 6H, adamantane-H), 7.27 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.46 (s, 1H, NH), 7.61 (d, 2H, *J* = 8.2 Hz, Ar-H). ^{13}C NMR: δ 27.86, 35.12, 36.46, 38.31 (adamantane-C), 117.35, 125.46, 130.02, 138.02 (Ar-C), 146.50 (C-8), 157.98 (C-5), 177.98 (C-2). MS, *m/z* (Rel. Int.): 378 (M^+ +2, 2), 375 (M^+, 5), 349 (4), 220 (28), 161 (49), 135 (68), 118 (17), 126 (100), 111 (44).

4e: ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 6H, adamantane-H), 2.01 (s, 3H, adamantane-H), 2.08 (s, 6H, adamantane-H), 7.45 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.51 (s, 1H, NH), 7.52 (d, 2H, *J* = 8.5 Hz, Ar-H). ^{13}C NMR: δ 27.86, 34.38, 36.45, 38.30 (adamantane-C), 115.01, 117.02, 131.71, 139.24 (Ar-C), 149.86 (C-8), 159.54 (C-5), 176.08 (C-2). MS, *m/z* (Rel. Int.): 431 (M^+ +2, 7), 429 (M^+, 5), 350 (3), 296 (18), 235 (12), 213 (11), 196 (9), 181 (19), 135 (100).

5-(1-Adamantyl)-2-amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (7): A mixture of cyanogen bromide (1.17 g, 11 mmol) and compound (**2**) (2.5 g, 10 mmol) in EtOH (30 mL) was heated under reflux for 4 h and the solvent was evaporated *in vacuo*. The residue was washed with saturated aqueous $NaHCO_3$ solution (10 mL), then with water, dried and crystallized from aqueous EtOH to yield 2.1 g (76%) of compound (**7**). Mp. 187-189 °C. ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 6H, adamantane-H), 2.03 (s, 3H, adamantane-H), 2.13 (s, 6H, adamantane-H), 6.14 (s, 2H, NH_2). ^{13}C NMR: δ 27.95, 35.14, 36.52, 39.02 (adamantane-C), 143.57 (C-8), 162.49 (C-5), 164.91 (C-2). MS, *m/z* (Rel. Int.): 275 (M^+, 100), 259 (61), 429 (3), 234 (23), 218 (28), 135 (86), 41 (96). Anal. Calcd for $C_{13}H_{17}N_5S$: C 56.70, H 6.22, N 25.43, S 11.64. Found C 56.48, H 6.41, N 25.35, S 11.50.

5-(1-Adamantyl)-2-substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (6a-e): ***Method A:*** The appropriate alkylisothiocyanate (2 mmol) was added to a solution of compound (**2**) (500 mg, 2 mmol) in dry DMF (8 mL) and the mixture was heated under reflux for 24 h. On cooling, the mixture was poured onto cold water (30 mL) and the separated precipitate was filtered, washed with water and crystallized to yield compounds (**6a-e**) in 51-63% yields. ***Method B:*** A mixture of the appropriate halide namely, methyl iodide, ethyl iodide, allyl bromide, *n*-butyl bromide or benzyl chloride (2 mmol), compound (**7**) (0.55 g, 2 mmol) and anhydrous K_2CO_3 (0.28 g, 2 mmol), in EtOH (10 mL) was heated under reflux for 2 h and the solvent was distilled off *in vacuo*. The obtained residue was washed with water, dried and crystallized.

6a: ^{1}H NMR ($CDCl_3$): δ 1.71 (s, 6H, adamantane-H), 1.98 (s, 3H, adamantane-H), 2.10 (s, 6H, adamantane-H), 3.59 (s, 3H, CH_3), 5.27 (s, 1H, NH). ^{13}C NMR: δ 27.83, 34.72, 35.99, 38.37 (adamantane-C), 39.05 (CH_3), 150.03 (C-8), 158.18 (C-5), 175.05 (C-2). MS, m/z (Rel. Int.): 289 (M^+, 26), 234 (87), 154 (11), 135 (100), 55 (92).

6b: ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 3H, *J* = 7.3 Hz, CH_3), 1.75 (s, 6H, adamantane-H), 1.93 (s, 3H, adamantane-H), 2.08 (s, 6H, adamantane-H), 3.32 (q, 2H, *J* = 7.3 Hz, $CH_3C\boldsymbol{H}_2$), 5.52 (s, 1H, NH). ^{13}C NMR: δ 14.25 (CH_3), 27.40, 34.21, 36.28, 39.32 (adamantane-C), 42.56 (CH_2NH), 150.11 (C-8), 157.12 (C-5), 176.73 (C-2). MS, *m/z* (Rel. Int.): 303 (M^+, 17), 234 (100), 135 (53), 104 (40), 90 (51), 60 (88).

6c: ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 6H, adamantane-H), 1.97 (s, 3H, adamantane-H), 2.12 (s, 6H, adamantane-H), 4.62 (s, 2H, CH_2), 4.75 (d, 1H, $=CH^a$, *J* = 17.6 Hz), 5.25-5.51 (m, 2H, $=CH^b$ & NH), 5.83-5.94 (m, 1H, -CH=). ^{13}C NMR: δ 27.53, 34.02, 36.15, 39.77 (adamantane-C), 66.01 (CH_2NH), 113.66 (CH_2=CH), 133.05 (CH_2=CH), 149.06 (C-8), 158.80 (C-5), 179.26 (C-2). MS, *m/z* (Rel. Int.): 315 (M^+, 2), 234 (21), 227 (24), 185 (31), 153 (88), 135 (61), 95 (72), 57 (100)**.**

6d: ^{1}H NMR ($CDCl_3$): δ 1.01 (t, 3H, *J* = 7.5 Hz, CH_3), 1.36-1.68 (m, 4H, CH_2CH_2), 1.73 (s, 6H, adamantane-H), 1.98-2.16 (m, 9H, adamantane-H), 3.18 (q, 2H, *J* = 7.5 Hz, $C\boldsymbol{H}_2NH$), 5.72 (s, 1H, NH). ^{13}C NMR: δ 14.72 (CH_3), 19.50 ($CH_3\boldsymbol{C}H_2$), 27.35, 32.85, 34.28, 35.88, 39.03 (adamantane-C & $\boldsymbol{C}H_2CH_2NH$), 58.52 (CH_2NH), 149.03 (C-8), 158.80 (C-5), 175.62 (C-2). MS, *m/z* (Rel. Int.): 331 (M^+, 3), 288 (5), 234 (100), 135 (52), 43 (48).

6e: ^{1}H NMR ($CDCl_3$): δ 1.76 (s, 6H, adamantane-H), 1.99 (s, 3H, adamantane-H), 2.12 (s, 6H, adamantane-H), 4.98 (s, 2H, $C_6H_5C\boldsymbol{H}_2$), 5.49 (s, 1H, NH), 7.15-7.32 (m, 5H, Ar-H). ^{13}C NMR: δ 27.42, 34.09, 36.15, 39.01 (adamantane-C), 65.50 ($C_6H_5\boldsymbol{C}H_2$), 124.57, 126.55, 130.02, 137.50 (Ar-C), 148.80 (C-8), 156.65 (C-5), 177.05 (C-2). MS, *m/z* (Rel. Int.): 365 (M^+, 3), 273 (8), 234 (100), 135 (82), 91 (94).

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