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Synthesis and characterization of carbamates derivatives from 4-amino-1,2,4-triazole

Sunil Kumar Choudhary[a], Monika Trivedi[a] & Nidhi Sogani[b,*]

[a] Department of Biotechnology and Allied Sciences, Faculty of Education and Methodology, Jayoti Vidyapeeth Women's University Jaipur 303 122, India

[b] Department of Chemistry, IIS University, Jaipur 302 020, India

*E-mail: nidhisogani2507@gmail.com

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Carbamate derivatives are proved to be an essential class of molecules because of their application as drugs and prodrugs. Their several derivatives also have been used to craft the drug-target interfaces by incorporating the carbamate moiety. Due to the huge demand in pharma-industries these have been extensively explored and synthesized. The synthesis and characterization of carbamate derivatives from 4-amino-1,2,4-triazoles and 3-(methylthio)-4-amino-1,2,4-triazoles are described. Carbamate derivatives of 4-amino-1,2,4-triazoles with phenyl chloroformate in CH_3CN using K_2CO_3 at *ca.* ~80°C have been synthesized with good to excellent yield (~81 to 97%). The methodology has been subsequently extended for synthesis of carbamate derivatives of 3-(methylthio)-4-amino-1,2,4-triazoles in which bicarbamate derivatives are formed as major products (~39 to 47%) along with mono carbamate derivatives as minor products (~9 to 22%) in the presence of similar solvent and base. On investigating the effect of solvent and base, the reaction in CH_3CN in presence of K_2CO_3 shows the best results.

Keywords: Carbamates, 4-Amino-1,2,4-triazole, Bicarbamates, 3-(Methylthio)-4-amino-1,2,4-triazole, Solvent effect, Base effect

Carbamate functionalities have been of interest due to their omnipresence in many natural products[1], pharmaceuticals[2] and agrochemicals[3]. Carbamates are also useful as protecting groups in peptide synthesis[4] and as intermediates in various organic syntheses[5]. These carbamate groups are used as protecting groups, toxophores in biologically active molecules or as prodrugs for better biochemical properties[6]. In literature, many methods have been reported for the synthesis of carbamates[7]. These preparations mainly include reacting chloroformates[8] or dialkyl carbonates[9] with amines, and alcohols with isocyanates[10a-d] or isocyanides[10e,f].

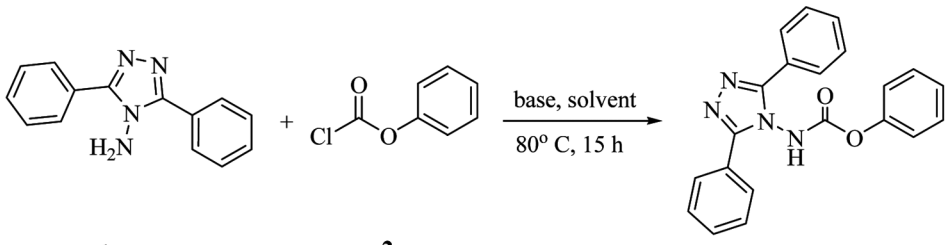
Triazoles are heterocyclic organic compounds having a five-membered ring molecular structure containing three nitrogen atoms. The chemistry of triazoles derivatives received much attention because of its application in medicine[11], agriculture[12] and industry[13]. Compounds containing 4-amino-1,2,4-triazole moiety have received considerable attention among chemists because molecules with these structural features have been found to display a wide range of biological activities, such as antifungal[14], antibacterial and antimicrobial[15].

The systematic literature survey reveals that there are lots of carbamates were reported on 1,2,4-triazole but there is not much carbamates were synthesized by using amino moiety of 4-amino-1,2,4-triazole. In this paper, a new series of 4-amino-1,2-4-triazole and 3-marcapto-4-amino-1,2-4-triazole based carbamates have been synthesized. Additionally, we also examined the effect of solvents and bases on above reaction.

Results and Discussion

Our initial attempt was to optimized the model reaction of 3,5-diphenyl-[1,2,4]-triazol-4-ylamine (**1a**) with phenyl chloroformate (**2**) at 80°C for 15 h to investigate the effect of base and solvent in synthesis of carbamate (Scheme 1, Table 1).

Interestingly, no reaction took place without bases (not shown in Table 1). In the presence of K_2CO_3 the reaction complete with the highest yield (Table 1, entry 1, 95%). Moderate yields obtained, when K_3PO_4, Et_3N and NaOH were used as bases (62%, 75% and 54%, respectively) (Table 1, entries 2, 3 and 4). As Cs_2CO_3 or Na_2CO_3 bases were added to this reaction system, the reaction proceeded to give the target product **3a** with low yields (42 and 45%, respectively) (Table 1, entries 5 and 6). The selection of solvents proved to have a dramatic influence on the reaction (Table 1, entries 1, 7-10). When the reaction was carried out in



1a **2** **3a**

Scheme 1 — Model reaction for optimization of solvent and base effect

ethanol, no reaction observed (Table 1, entry 10). Other solvents such as CH_3CN, THF, Dioxane and DMF, resulted in good yields (95%, 72%, 64% and 50%, respectively) (Table 1, entries 1, 7-9).

With the optimal reaction conditions, we carried out the reactions of 4-amino-1,2,4-triazoles (**1a-g**) with **2** in CH_3CN using K_2CO_3 at *ca*. ~80°C to synthesize carbamate derivatives (**3a-g**) in good to excellent yield (~81 to 97%) (Scheme 2, Table 2). All the products are off-white solid, which have been characterized on the basis of spectral and elemental analysis.

On the basis of above results, the reactions of 3-(methylthio)-4-amino-1,2,4-triazole derivatives (**4a-c**) with **2** were also investigated in the presence of similar solvent and base (Scheme 3). Interestingly, these reactions afford bicarbamate derivatives (**5a-c**) as major products (~39 to 47%) along with mono carbamate derivatives (**6a-c**) as minor products (~9 to 22%) (Table 3), which were separated chromatographically and characterized using spectral and elemental analysis. In ^{1}H NMR spectra of **6a-c**, a singlet peak of -NH at δ 12.01 to 8.89 is observed which confirms the formations of mono carbamate derivatives. Whereas in **5a-c**, this peak is absence which confirms the absence of –NH moiety and formation of bicarbamates.

Table 1 — Effects of bases and solvents (Scheme 1)

Entry	Base	Solvent	Yield of **3a** (%)
1	K_2CO_3	CH_3CN	95%
2	K_3PO_4	CH_3CN	62%
3	TEA	CH_3CN	75%
4	NaOH	CH_3CN	54%
5	Cs_2CO_3	CH_3CN	42%
6	Na_2CO_3	CH_3CN	45%
7	K_2CO_3	THF	72%
8	K_2CO_3	Dioxane	64%
9	K_2CO_3	DMF	50%
10	K_2CO_3	Ethanol	Nil

Table 2 — Synthesis of carbamate derivatives of 4-amino-1,2,4-triazoles (Scheme 2)

Entry	Compd	R	R^1	Yield (%)
1	**3a**	H	H	95
2	**3b**	3-Cl	H	94
3	**3c**	2-Cl	H	93
4	**3d**	3-F	H	94
5	**3e**	3,5-$(Me)_2$	H	81
6	**3f**	3,5-$(Me)_2$	3-F	94
7	**3g**	3,5-$(Me)_2$	2-Cl	97

Table 3 — Synthesis of carbamate derivatives of 3-(methylthio)-4-amino-1,2,4-triazoles (Scheme 3)

Entry	Compd	R	Yield (%)	
			5 (Major)	**6** (Minor)
1	**a**	H	47	22
2	**b**	2-Cl	41	15
3	**c**	4-Br	39	9

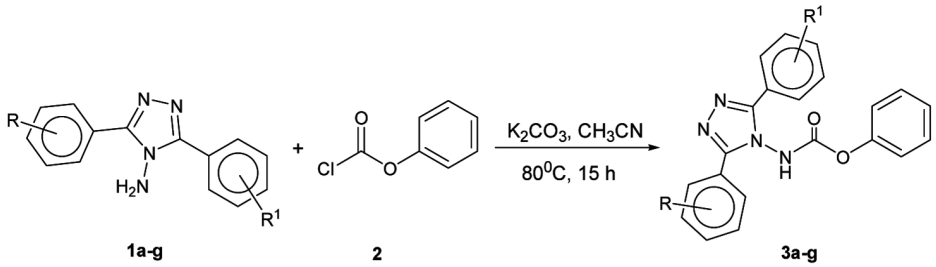
Experimental Section

Commercially available reagents were used without further purification. Solvents were freshly dried and distilled. All the reactions were monitored by TLC on pre-coated silica gel plates. Silica gel (60-80 Mesh) for column chromatography and anhydrous sodium sulphate were activated in muffle furnace before use.

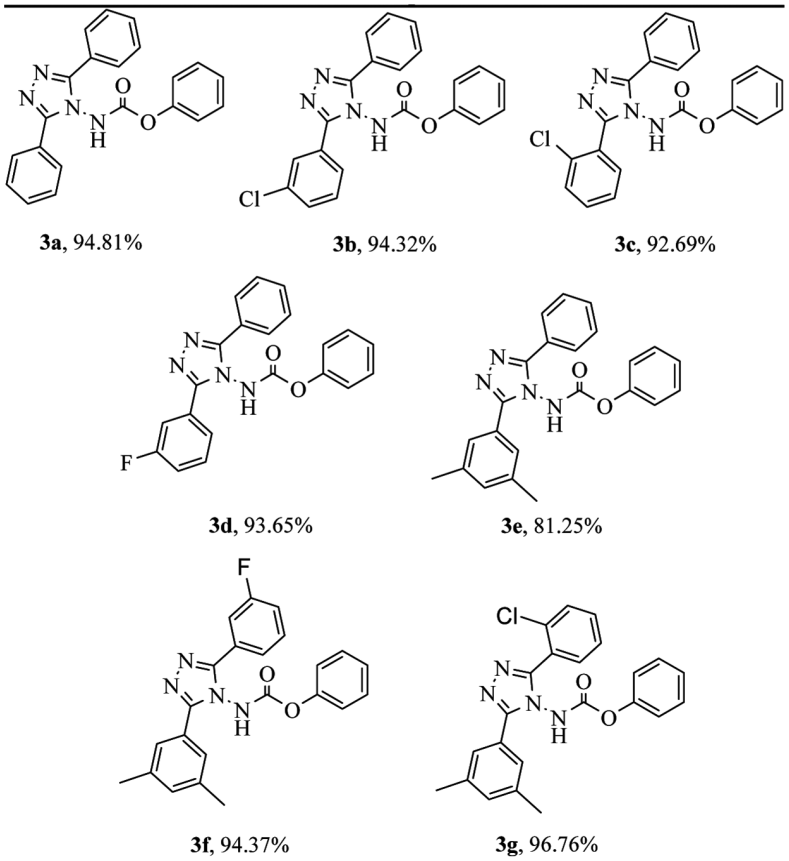
Melting points were determined on a Tempo apparatus and are uncorrected. NMR spectra were recorded on a Bruker-DPX-300 (300 MHz) spectrometer. ^{1}H NMR at a frequency of 300 MHz and ^{13}C NMR at a frequency of 100 MHz (using TMS as the internal reference). The C,H,N elemental analyses were done on FLASH Ea 1112 series CHN analyzer. Mass spectra were recorded on Xevo G2-S Q Tof (Waters, USA) mass spectrometer.

General procedure and characterization data for the synthesis of carbamate derivatives, 3a-3g, 5a-5c and 6a-6c

4-Amino-1,2,4-triazole derivatives (1.0 g, 3.69 mmol) was dissolved in acetonitrile (20 mL, 20 vol. eq.) taken in 100 mL in round bottom flask. Potassium carbonate (1.45 g, 9.23 mmol, 2.5 eq.) and phenyl chloroformate (0.58 g, 3.69 mmol, 1.0 eq.)



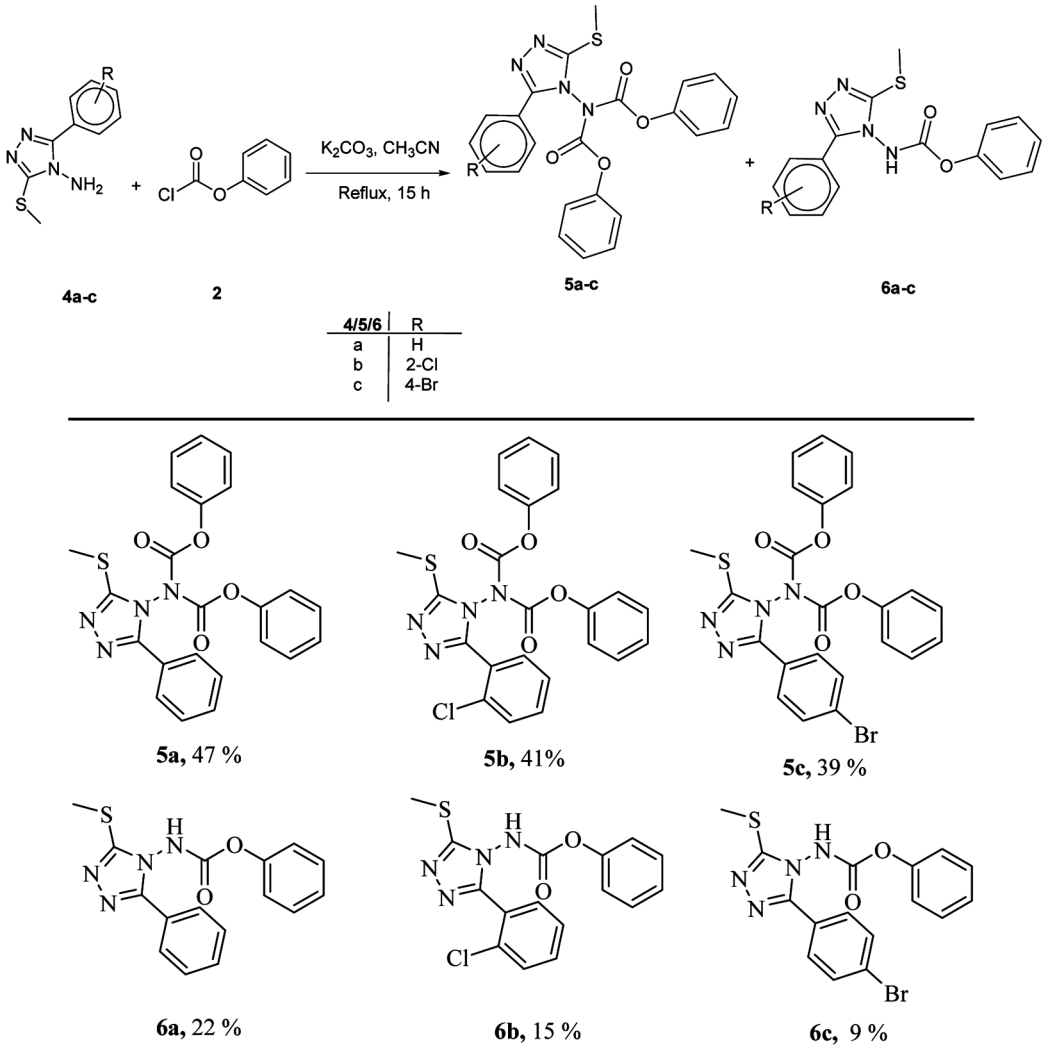
1/3	R	R^1
a	H	H
b	3-Cl	H
c	2-Cl	H
d	3-F	H
e	3,5-$(Me)_2$	H
f	3,5-$(Me)_2$	3-F
g	3,5-$(Me)_2$	2-Cl



Scheme 2 — Synthesis of carbamate derivatives of 4-amino-1,2,4-triazoles

were added to this solution and the reaction mixture was refluxed for 15 h with constant stirring. The progress of the reaction was monitored by Thin Layer Chromatography (TLC) (solvent: *n*-hexane:EtOAc:: 40:60 v/v%). After the completion of the reaction, the reaction mixture was quenched with distilled water (50 mL). The product was extracted with ethyl acetate (3×50 mL) and washed with brine (100 mL). The combined organic layer was dried over anhydrous sodium sulphate. The solvent was removed under a reduced pressure, and the residue was purified by column chromatography over silica gel (200–300 mesh) using ethyl acetate/*n*-hexane as the eluent to afford the desired products as an off white solid.

Phenyl (3,5-diphenyl-4*H*-1,2,4-triazol-4-yl)carbamate, 3a: Following general procedure, the product **3a** was obtained as an off-white solid. m.p. 152-



Scheme 3 — Synthesis of carbamate derivatives of 3-(methylthio)-4-amino-1,2,4-triazoles

154°C. Yield 95%. R_f 0.50 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 7.86 – 7.74 (m, 8H), 7.46 – 7.31 (m, 5H), 6.88 (dd, *J* = 7.8, 1.7 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25°C): δ 153.8, 149.7, 148.3, 131.3, 129.7 (d, *J*=43.0 Hz), 128.3, 127.2,125.3, 120.7. Anal. Calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72. Found: C, 70.92; H, 4.38; N, 15.64%. MS: *m/z* Calcd: 356.4. Found: 355.0 (M-1), 356.8 (M+1).

Phenyl (3-(3-chlorophenyl)-5-phenyl-4*H*-1,2,4-triazol-4-yl)carbamate, 3b: Following general procedure, the product **3b** was obtained as an off-white solid. m.p. 185-187°C. Yield 94%. R_f 0.60 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 12.25 (s, 1H), 8.00 – 7.85 (m, 2H), 7.85 (dd, *J* = 5.2, 3.1 Hz, 3H), 7.73 – 7.65 (m, 4H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 6.0 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.5 Hz, 2H). Anal. Calcd for $C_{21}H_{15}ClN_4O_2$: C, 64.54; H, 3.87; Cl, 9.07; N, 14.34. Found: C, 64.68; H, 3.72; Cl, 8.98; N, 14.26%. MS: *m/z* Calcd: 390.8. Found: 388.9, 390.0 (3:1) (M-1), 390.6, 392.8 (3:1) (M+1).

Phenyl (3-(2-chlorophenyl)-5-phenyl-4*H*-1,2,4-triazol-4-yl)carbamate, 3c: Following general procedure, the product **3c** was obtained as an off-white solid. m.p. 196-197°C. Yield 93%. R_f 0.48 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz. DMSO-d_6, 25°C): δ 9.33 (s, 1H), 9.15 (s, 2H), 7.81-7.74 (m, 4H), 7.48-7.35 (m, 8H); ^{13}C NMR (100 MHz. DMSO-d_6, 25°C): δ 155.4, 154.7, 153.5, 132.6, 131.7(d, *J*=31.0 Hz), 130.2, 129.1, 127.2, 125.9, 123.8, 122.6. Anal. Calcd for $C_{21}H_{15}ClN_4O_2$: C,

64.54; H, 3.87; Cl, 9.07; N, 14.34. Found: C, 64.47; H, 3.96; Cl, 8.99; N, 14.46%. MS: *m/z* Calcd: 390.8. Found: 388.2, 390.6 (3:1) (M-1), 391.8, 393.2 (3:1) (M+1).

Phenyl (3-(3-fluorophenyl)-5-phenyl-4*H*-1,2,4-triazol-4-yl)carbamate, 3d: Following general procedure, the product **3d** was obtained as an off-white solid. m.p. 192-194°C. Yield 94%. R_f 0.55 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 7.93 – 7.60 (m, 7H), 7.47 – 7.31 (m, 5H), 6.94 – 6.88 (m, 3H); ^{13}C NMR (100 MHz. DMSO-d_6, 25°C): δ 164.2, 161.8, 154.0 (d, *J*=36.0 Hz), 152.7, 149.7, 148.3, 131.4, 129.8 (d, *J*=45.9 Hz), 128.3, 127.4, 123.8, 120.6, 118.5 (d, *J*=21.0 Hz), 115.3 (d, *J*=24.0 Hz). Anal. Calcd for $C_{21}H_{15}FN_4O_2$: C, 67.37; H, 4.04; F, 5.07; N, 14.97. Found: C, 67.42; H, 3.96; F, 4.98; N, 14.84%. MS: *m/z* Calcd: 374.4. Found: 373.1 (M-1).

Phenyl (3-(3,5-dimethylphenyl)-5-phenyl-4*H*-1,2,4-triazol-4-yl)carbamate, 3e: Following general procedure, the product **3e** was obtained as an off-white solid. m.p. 177-178°C. Yield 81%. R_f 0.51 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 7.85 (dd, *J* = 6.7, 2.8 Hz, 2H), 7.76 – 7.73 (m, 2H), 7.45 – 7.30 (m, 5H), 6.90 (dd, *J* = 7.7, 1.7 Hz, 4H), 2.42 (s, 6H); ^{13}C NMR (100 MHz. DMSO-d_6, 25°C): δ 154.3, 153.7, 149.7, 148.3, 139.2, 138.4, 133.1, 132.2, 131.4, 129.7 (d, *J*=43.0 Hz), 128.5 (t, *J*=22.0 Hz), 127.1 (d, *J*=25.0 Hz). 126.2 (d, *J*=17.0 Hz), 121.1 (d, *J*=20.0 Hz), 120.7, 115.7, 21.4 (d, *J*=27.0 Hz). Anal. Calcd for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57. Found: C, 71.65; H, 5.37; N, 14.31%. MS: *m/z* Calcd: 384.8. Found: 383.3 (M-1).

Phenyl (3-(3,5-dimethylphenyl)-5-(3-fluorophenyl)-4*H*-1,2,4-triazol-4-yl)carbamate, 3f: Following general procedure, the product **3f** was obtained as an off-white solid. m.p. 204-206°C. Yield 94%. R_f 0.45 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 7.45 – 7.32 (m, 9H), 6.93 (d, 4H), 2.49 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz. DMSO-d_6, 25°C): δ 164.0 (d, *J*=36.0 Hz), 161.6 (d, *J*=34.0 Hz), 156.4, 154.8, 153.3, 150.3, 149.7, 148.3, 139.3, 138.6, 133.4, 132.7, 131.4 (d, *J*=8.0 Hz), 130.3 (d, *J*=8.0 Hz), 130.0, 129.6 (t, *J*=13.0, *J*=8.0 Hz), 127.4, 126.2 (t, *J*=14.0 Hz), 124.3 (t, *J*=16.0, *J*=9.0 Hz), 123.8, 121.7, 121.1, 120.6, 120.1, 118.7 (d, *J*=21.0 Hz), 117.7 (d, *J*=21.0 Hz), 115.5 (d, *J*=23.0 Hz). Anal. Calcd for $C_{23}H_{19}FN_4O_2$: C, 68.65; H, 4.76; F, 4.72; N, 13.92. Found: C, 68.82; H, 4.64; F, 4.81; N, 13.77%. MS: *m/z* Calcd: 402.4. Found: 401.2 (M-1).

Phenyl (3-(2-chlorophenyl)-5-(3,5-dime-thylphenyl)-4*H*-1,2,4-triazol-4-yl)carbamate, 3g: Following general procedure, the product **3g** was obtained as an off-white solid. m.p. 198-200°C. Yield 97%. R_f 0.50 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 7.46 (t, *J* = 7.7 Hz, 4H), 7.40 – 7.33 (m, 4H), 6.88 (d, *J* = 7.9 Hz, 4H), 2.42 (s, 6H). Anal. Calcd for $C_{23}H_{19}ClN_4O_2$: C, 65.95; H, 4.57; Cl, 8.46; N, 13.38. Found: C, 65.72; H, 4.90; Cl, 8.28; N, 13.24%. MS: *m/z* Calcd: 418.9. Found: 416.8, 418.2 (3:1) (M-1).

Phenyl (3-(methylthio)-5-phenyl-4*H*-1,2,4-triazol-4-yl)dicarbamate, 5a: Following general procedure, the major product **5a** was obtained as an off-white solid. m.p. 220-222°C. Yield 47%. R_f 0.42 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 7.80 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.71(t, 3H), 7.48 (t, *J* = 7.7 Hz, 4H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.13 (d, *J* = 7.7 Hz, 4H), 2.81 (s, 3H). Anal. Calcd for $C_{23}H_{18}N_4O_4S$: C, 61.87; H, 4.06; N, 12.55; S, 7.18. Found: C, 61.72; H, 4.24; N, 12.37; S, 7.02%.

Phenyl (3-(methylthio)-5-phenyl-4*H*-1,2,4-triazol-4-yl)carbamate, 6a: Following general procedure, the product minor **6a** was obtained as an off-white solid. m.p. 186-188°C. Yield 22%. R_f 0.63 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 8.89 (s, 1H), 7.71 (s, 2H), 7.43 (d, *J* = 5.9 Hz, 3H), 7.20 (d, *J* = 8.2 Hz, 3H), 7.11 (t, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 3.50 (s, 3H). Anal. Calcd for $C_{16}H_{14}N_4O_2S$: C, 58.88; H, 4.32; N, 17.17; S, 9.82. Found: C, 58.76; H, 4.47; N, 16.98; S, 9.73%. MS: *m/z* Calcd: 326.1. Found: 324.9 (M-1).

Phenyl (3-(2-chlorophenyl)-5-(methylthio)-4*H*-1,2,4-triazol-4-yl)dicarbamate, 5b: Following general procedure, the product major **5b** was obtained as an off white solid. m.p. 227-229°C. Yield 41%. R_f 0.45 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.51 – 7.42 (m, 3H), 7.37 – 7.29 (m, 4H), 7.25 – 7.19 (m, 3H), 7.04– 6.95 (m, 4H), 2.80 (s, 3H). Anal. Calcd for $C_{23}H_{17}ClN_4O_4S$: C, 57.44; H, 3.56; Cl, 7.37; N, 11.65; S, 6.67. Found: C, 57.32; H, 3.67; Cl, 7.24; N, 11.56; S, 6.84%.

Phenyl (3-(2-chlorophenyl)-5-(methylthio)-4*H*-1,2,4-triazol-4-yl)carbamate, 6b: Following general procedure, the product minor **6b** was obtained as an off white solid. m.p. 201-203°C. Yield 15%. R_f 0.62 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 11.86 (s, 1H), 7.79 – 7.33 (m, 6H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.08 – 6.82 (m, 2H), 2.71 (s, 3H). Anal. Calcd for $C_{16}H_{13}ClN_4O_2S$: C, 53.26; H, 3.63; Cl, 9.83; N, 15.53; S, 8.89. Found: C, 53.14; H, 3.81; Cl, 9.64; N, 15.46; S, 8.97%. MS: *m/z* Calcd: 360.0. Found: 359.1, 360.9 (3:1) (M-1).

Phenyl (3-(4-bromophenyl)-5-(methylthio)-4*H*-1,2,4-triazol-4-yl)dicarbamate, 5c: Following general procedure, the product major **5c** was obtained as an off white solid. m.p. 225-227°C. Yield 39%. R_f 0.40 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.68 – 7.53 (m, 3H), 7.39 – 7.26 (m, 4H), 7.26 – 7.11 (m, 3H), 7.07 – 6.91 (m, 4H), 2.78 (s, 3H). Anal. Calcd for $C_{23}H_{17}BrN_4O_4S$: C, 52.58; H, 3.26; Br, 15.21; N, 10.66; S, 6.10. Found: C, 52.44; H, 3.48; Br, 15.03; N, 10.54; S, 5.85%.

Phenyl (3-(4-bromophenyl)-5-(methylthio)-4*H*-1,2,4-triazol-4-yl)carbamate, 6c: Following general procedure, the product minor **6c** was obtained as an off-white solid. m.p. 192-194°C. Yield 9%. R_f 0.54 (hexane:ethyl acetate 2:3); ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ 12.01 (s, 1H), 7.80 (dd, *J* = 33.4, 8.5 Hz, 4H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 2.69 (s, 3H). Anal. Calcd for $C_{16}H_{13}BrN_4O_2S$: C, 47.42; H, 3.23; Br, 19.72; N, 13.82; S, 7.91. Found: C, 47.68; H, 3.49; Br, 19.64; N, 13.69; S, 7.76%. MS: *m/z* Calcd: 406.0. Found: 404.9, 406.6 (1:1) (M-1).

Conclusion

Carbamate derivatives of 4-amino-1,2-4-triazoles were synthesized from the reaction of 4-amino-1,2-4-triazole substrates with phenyl chloroformate in good to excellent yield (81 to 97%). The methodology was subsequently extended for synthesis carbamate derivatives of 3-(methylthio)-4-amino-1,2,4-triazoles through the reaction of 3-(methylthio)-4-amino-1,2,4-triazole substrates with phenyl chloroformate in which bicarbamate formed as major product (~39 to 47%) whereas monocarbamate as minor one (~9 to 22%). While investigating the effect of solvent and base, the reaction in CH_3CN on using K_2CO_3 showed the best results.

Acknowledgements

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