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Synthesis of 3(5)-Substituted 1,2,4-Triazoles by Lithiation of 1-(1-Pyrrolidinomethyl)-1,2,4-triazole[1]

Alan R. Katritzky*, Ping Lue, and Konstantina Yannakopoulou
Department of Chemistry, University of Florida, Gainesville, FL 32611, U. S. A.
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Abstract: *1,2,4-Triazole* ***1*** *is readily converted into 3(5)-substituted 1,2,4-triazoles* ***4*** *by a three-step sequence: (i) Mannich reaction with formaldehyde and pyrrolidine; (ii) lithiation of 1-(1-pyrrolidinomethyl)-1,2,4-triazole* ***2****, followed by addition of an electrophile; (iii) deprotection of the N-aminal groups of the N-protected 3-substituted 1,2,4-triazoles* ***3*** *using sodium borohydride ($NaBH_4$) in ethanol. 3(5)-Substituted 1,2,4-triazoles* ***4*** *result in good overall yields.*

3(5)-Substituted 1,2,4-triazoles are important heterocyclic compounds with many important industrial applications.[2] Numerous publications, mainly patents, demonstrate their use in agriculture, pharmacy, dyestuffs, photography, and polymers.[2] Given this importance, preparative methods are in continuous development. The classical route to 3(5)-substituted 1,2,4-triazoles is based on the cyclization of a suitable acyclic precursor.[2] Other methods include: (i) the removal of a 5-thione or 5-amino group from a preformed 3- or 5- substituted triazole,[3-4] (ii) ring interconversion of heterocycles (e.g. 4,6-disubstituted pyrimidines and s-triazines) into 3(5)-substituted 1,2,4-triazoles.[5] However, all these methods suffer from disadvantages including: (i) the nature of the 3(5)-substituents introduced is limited by the transformation conditions of an acyclic precursor,[2] (ii) the conditions for the removal of thione and amino groups is incompatible with some substituents,[3-4] (iii) isomer mixtures can arise in ring transformations.[5]

It is well known that 1-substituted 1,2,4-triazoles undergo lithiation rapidly at the 5-position.[6] For example, 1-benzyl-3-phenyl-1,2,4-triazole readily forms a 5-lithio species which reacts with benzophenone to give the corresponding alcohol in high yield (92%).[7] Again, the lithiation of 1-(2-pyridyl)-1,2,4-triazole gives exclusively the C-5 lithio species which undergoes oxidative coupling in the presence of copper chloride to give the 5,5′-bistriazole.[8] Hence, lithiation represents a very useful route for the preparation of 1,5-disubstituted 1,2,4-triazoles. However, N-unsubstituted triazoles cannot be C-lithiated as they form unreactive N-anions. Little previous work has appeared on the use of N-protecting group to enable C-lithiation in the 1,2,4-triazole series, followed by removal of the N-protecting group. Benzyl has been reported as an efficient N-protecting group for 1,2,4-triazoles and successful C-lithiation can be achieved.[7,9,10] However, the removal of a benzyl group usually requires rather strong conditions such as reductive cleavage by sodium in liquid ammonia[7,9,10] or hydrogenolysis with Pd-C under pressure.[10] Methyl could be used as a N-protecting group from the point of view of its easy introduction, but removal of methyl cannot be achieved under normal conditions.[10,11] Recently, the triphenylmethyl group has been

used as protecting group for 1,2,4-triazole but the steric hindrance as well as the difficulty of removal under normal conditions makes it unsuitable for synthetic purposes.[10]

Continuation of our studies on the generation of heterocyclic carbanions, by the lithiation of an N-protected heterocycle, led us to search for suitable methodology to apply to the synthesis of 3(5)-substituted N-unsubstituted 1,2,4-triazoles. We have recently demonstrated[1] that such C-lithiation can be achieved in the case of benzimidazole, imidazole, and pyrazole, by using N-dialkylaminomethyl (aminal) protecting groups. In all these cases, lithiation occurs smoothly and cleanly at the alpha C-position and, after reaction with an electrophile, the protecting group was easily removed under mild hydrolytic conditions. We now report the successful extension of a modification of this method to the synthesis of 3(5)-substituted 1,2,4-triazoles.

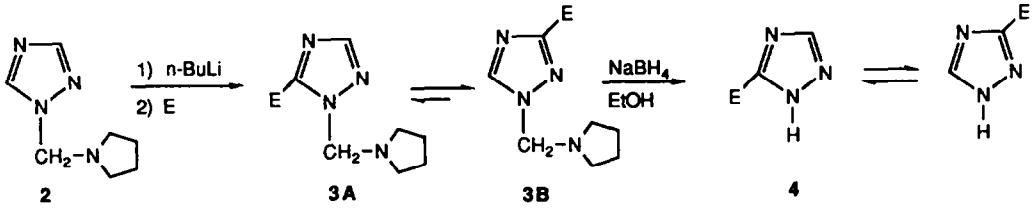
Results and Discussion

Synthesis: Similarly to the preparation of dialkylaminomethyl derivatives of other N-unsubstituted azoles, 1-(dialkylaminomethyl)-1,2,4-triazoles are easily prepared in bulk under Mannich reaction conditions.[12] We developed our own procedure, and prepared 1-(pyrrolidinomethyl)-1,2,4-triazole **2** in high yield (82%) from the parent triazole **1**, formaldehyde and pyrrolidine in refluxing ethanol.

The protected triazole **2** was treated with 1.1 equiv. of n-butyllithium in tetrahydrofuran at -78°C (the lithio salt of **2** was found to be more soluble in tetrahydrofuran than in diethyl ether), followed by quenching with D_2O. However, the product isolated was shown by nmr analysis as a mixture of two isomers (C-3 and C-5 deutero). In compound **2**, two different ring proton signals and the CH_2 proton signal appear at 7.98 (H-3), 8.24 (H-5) and at 5.19 ppm (CH_2) in ratio of 1:1:2. The proton nmr spectrum of the deutered compound **3b** also shows two different ring proton signals (7.98 ppm, H-3; and 8.25 ppm, H-5) and the CH_2 proton signal (5.19 ppm), but now in a ratio of 1:1:4, clearly indicating two isomers in a precisely 1:1 ratio. A similar result is observed for **3c** where a methyl group is incorporated into the ring. The proton nmr spectrum of **3c** also shows two different ring proton signals at 7.98 (H-3) and 8.20 ppm (H-5). However, unlike **3b**, two different CH_2 signals are now observed at 5.15 ppm and at 5.09 ppm and the amounts of the two isomers are unequal with the 3-substituted isomer slightly in excess ratio (ca. 10:9). Interestingly, further investigation with other electrophiles such as ketones and isocyanates showed that the reaction gave predominantly 3-substituted N-(pyrrolidinomethyl) -1,2,4-triazoles (Table 1). The evidence for these structures is again based on the nmr spectral data. From the literature, the ^{13}C nmr chemical shifts of solid 1H-1,2,4-triazole appear at 148.0 ppm (C-3) and 143.9 ppm (C-5).[13] This is in good correlation to the ^{13}C nmr chemical shifts of 1-methyl-1,2,4-triazole in solution (150.4 ppm, C-3; and 143.5 ppm, C-5).[14] Hence, in compound **2**, the downfield signal at 150.9 ppm is assigned to C-3 and the upfield signal at 143.0 ppm assigned to C-5. After lithiation, the ^{13}C nmr spectra of the products isolated (**3a**, **3d**, **3g**) all show the C-3 signal to be very much weaker than the C-5 signal. Similar results were observed with the proton spectra. Further proof has been taken from an X-ray crystal structure analysis of **3a** which verified that the substituent was introduced into C-3.[15]

These results were at first surprising since we expected that the reaction should give 5-substituted products, based on the literature. Literature precedents in the lithiation of N-substituted 1,2,4-triazoles suggest that lithiation at C-5 position is predominant. Recently, this regioselectivity has been further confirmed by the X-ray structure analysis of the product of 1-benzyl-1,2,4-triazole.[10] Even in the hindered 1-triphenylmethyl-1,2,4-triazole, the lithiation occurs exclusively at C-5.[10] In our case, the aminal group should stabilize the adjacent carbanion by complexing the lithium atom and thus, lithiation of **2** is certainly expected to occur at C-5 rather than at C-3.

These unexpected results suggested that a isomerization process probably exists between 5-substituted **3A** and 3-substituted **3B** (Scheme 1): the lithiation surely results in the formation of **3A**, but subsequent isomerization favors structurally more stable **3B** because of its less steric hindrance. Such isomerizations have been well studied with N-(aminoalkyl) benzotriazoles[16,17] and have been reported for a few other azoles.[13,18] To confirm such isomerization in N-aminoalkyl-1,2,4-triazoles, a detailed kinetic nmr study was carried out and the results obtained confirmed our hypothesis.[15]



2 **3A** **3B** **4**

Scheme 1

Table 1. Preparation of Substituted 1-Pyrrolidinomethyl-1,2,4-triazoles 3 from 2

Compd	Electrophile[a]	3-Substituent	Yield (%)[b]	mp[c]	Formula	Found(calcd) C	H	N
3a	Cyclohexanone	$(CH_2)_5COH$	83	126-128	$C_{13}H_{22}N_4$	62.73 (62.37)	8.86 (8.86)	22.20 (22.38)
3b	D_2O	D	90	oil	$C_7H_{11}DN_4$	152.1038[d]	(152.1046)	
3c	CH_3I	CH_3	95	oil	$C_8H_{14}N_4$	165.1142[e]	(165.1140)	
3d	$(CH_3)_3CNCO$	$(CH_3)_3CNHCO$	86	128-130	$C_{12}H_{21}N_5O$	57.70 (57.35)	8.52 (8.42)	27.95 (27.86)
3e	C_6H_5CHO	C_6H_5CHOH	87	83-85	$C_{14}H_{18}N_4O$	65.08 (65.08)	7.12 (7.02)	21.88 (21.69)
3f	$4\text{-}CH_3C_6H_4CHO$	$4\text{-}CH_3C_6H_4CHOH$	78	98-100	$C_{15}H_{20}N_4O$	65.96 (66.15)	7.40 (7.40)	20.78 (20.57)
3g	C_6H_5NCO	C_6H_5NHCO	91	110-112	$C_{14}H_{17}N_5O$	62.34 (61.98)	5.96 (6.32)	25.99 (25.81)

[a] 1.0 to 1.1 eq. of electrophile was added at -78°C. [b] Isolated yield. [c] Uncorrected. [d] MS (HR) for $C_7H_{10}DN_4$ $(M-1)^+$. [e] MS (HR).

Table 2. ^{1}H-NMR Chemical Shifts (δ) for Substituted 1-(Pyrrolidinomethyl)-1,2,4-triazoles 3 (ppm)

Compd	Triazole Ring		NCH_2N	Pyrrolidino Ring		Other signals
	H-3	H-5		α	β	
3aB	-	8.09[a]	5.12	2.73[b]	.[c]	1.21-2.21 (m, 14 H) 3.98 (bs, 1 H, OH)
3bA	7.98[a]	-	5.19	2.76[b]	1.78[b]	-
3bB	-	8.25[a]	5.19	2.76[b]	1.78[b]	-
3cA	7.98[a]	-	5.09	2.78[b]	1.78[b]	2.58 (s, 3 H, CH_3)
3cB	-	8.20[a]	5.15	2.78[b]	1.78[b]	2.39 (s, 3 H, CH_3)
3dB	-	8.31[a]	5.21	2.72[b]	1.75[b]	1.48 (s, 9 H, CH_3) 7.08 (s, 1 H, NH)
3eA	7.78[a]	-	4.55[d]	2.57[b]	1.81[b]	6.10 (s, 1 H, CH) 7.26-7.48 (m, 5 H)
3eB	-	8.43[a]	5.06	2.59[b]	1.59[b]	5.91 (s, 1 H, CH) 7.26-7.48 (m, 5 H)
3fA	7.77[a]	-	4.56[e]	2.58[b]	1.81[b]	2.34 (s, 3 H, CH_3) 6.05 (s, 1 H, CH) 7.17 (d, J = 8 Hz, 2H) 7.23 (d, J = 8 Hz, 2 H)
3fB	-	8.42[a]	5.05	2.59[b]	1.59[b]	2.31 (s, 3 H, CH_3) 5.88 (s, 1 H, CH) 7.14 (d, J = 8 Hz, 2 H) 7.36 (d, J = 8 Hz, 2H)
3gB	-	8.81[a]	5.27	2.66[b]	1.65[b]	7.12-7.39 (m, 3 H) 7.84 (m, 2 H) 10.39 (s, 1 H, NH)

[a] Singlet. [b] Multiplet, 4 H. [c] Immersed in the other protons. [d] dd, J = 12 Hz. [e] dd, J = 12 Hz.

Several 3-substituted N-protected triazoles 3 were isolated and characterized. Table 1 gives the isolated yields of the various products along with mp/bp data, and shows the range of electrophiles employed. Substituents introduced in this way into the 3-position of 1,2,4-triazole include an alkyl group from an alkyl halide; hydroxyalkyl from aldehydes and ketones; carbamoyl from isocyanates; alkylthio from alkyl disulfides; and deuterium from D_2O. The yields are good to excellent and the procedures are simple. The new compounds are characterized by their ^{1}H (Table 2), ^{13}C (Table 3) nmr spectra and by elemental analysis (Table 1).

Table 3. ^{13}C-NMR Chemical Shifts (δ) for Substituted 1-(Pyrrolidinomethyl)-1,2,4-triazoles 3 (ppm)

Compd	Triazole Ring		NCH_2N	Pyrrolidino Ring		3-Substituent					
	C-3	C-5		β	α						
3aB	169.6	143.5	66.4	23.7	49.8	21.8	25.3	37.2	70.3		
3bA	150.8	143.0	65.8	23.2	49.1						
3bB	150.8	143.0	65.8	23.2	49.1						
3cA	148.9	159.3	64.1	22.4	48.9	12.6					
3cB	151.4	143.0	64.9	22.3	48.6	10.7					
3dB	157.2	144.1	67.0	23.5	49.5	28.4	51.2	158.2			
3eA	149.3	157.4	66.6	23.3	50.9	68.0	125.4	127.6	127.8	139.8	
3eB	165.4	145.1	69.1	23.4	49.0	68.0	126.5	126.9	127.8	143.1	
3fA	149.3	157.6	67.9	23.3	50.9	21.0	68.0	125.3	129.1	136.8	137.5
3fB	165.6	144.0	66.6	23.7	49.8	21.3	70.3	126.6	128.7	137.3	138.8
3gB	156.7	146.0	66.2	23.5	49.0	120.5	124.0	128.7	138.3	157.6	

However, when diphenyl disulfide was used as electrophile, deprotected 3(5)-phenylthio-1,2,4-triazole **4i** was the only product isolated under the normal work-up conditions (aq. NH_4Cl). Similarly, **4j** was obtained with dibenzyl disulfide as electrophile. Nucleophilic cleavage of the aminal by organosulfide anions formed in the reaction, forming stable thioaminals, presumably occurs. Such replacement is known in the case of benzotriazole adducts.[19] In a test reaction, equimolar amounts of **2** and sodium thiophenate were mixed and ^1H and ^{13}C nmr spectra recorded. New peaks at 4.65 ppm (CH_2, ^1H nmr) and at 62.5 ppm ($\underline{C}H_2$, ^{13}C nmr) were observed, arising from thioaminal. The chemical shifts were in good agreement with those of N-(phenylthiomethyl)pyrrolidine, independently prepared from formaldehyde, pyrrolidine and sodium thiophenate.

Deprotection: Hydrolysis of the protecting aminal groups in the case of 1-(dialkylaminomethyl)-benzimidazoles, -imidazoles and -pyrazoles is facile at 20°C using 2N hydrochloric acid during the workup.[1,20] Surprisingly, hydrolysis of such aminal groups in 1-(pyrrolidinomethyl)-1,2,4-triazoles is more difficult. Hydrochloric acid (2N) at 20°C cleaved the N-C bond only for diphenylhydroxymethyl substituted triazole **4h**, in which the aminal group was hydrolysed smoothly. Attempted deprotection using hydrochloric acid (2N) in refluxing ethanol for 12 hrs, left compound **2** unchanged. Compound **3a** was also unaffected under the same conditions, as indicated by the proton nmr spectrum. Since the acid-catalyzed hydrolysis of the aminal group is difficult for 1,2,4-triazoles, we turned to deprotection under reductive conditions. The N-substituents of N-(dialkylaminomethyl) benzotriazoles are easily cleaved with sodium borohydride ($NaBH_4$) in ethanol to give free benzotriazole and the N-methyldialkylamines.[21-23] Indeed, deprotection was readily accomplished when our N-protected 3-substituted 1,2,4-triazoles are heated with $NaBH_4$ in ethanol for few hours (Scheme 1). Table 4 gives the detailed results of the use of $NaBH_4$ as deprotecting reagent for the N-protected triazoles.

Table 4. Preparation of N-Unsubstituted 3(5)-Substituted-1,2,4-triazoles 4

Compd	3(5)-Substituent	Yield (%)[a]	mp[b]	Formula	Found(cacld) C	H	N
4a	$(CH_2)_5COH$	98[c]	183-185	$C_8H_{13}N_3O$	57.32 (57.47)	8.00 (7.84)	25.41 (25.13)
4c	CH_3	90[c]	92-94[e]	$C_3H_5N_3$	-	-	-
4d	$(CH_3)_3CNHCO$	95[c]	175-177	$C_7H_{12}N_4O$	49.67 (49.99)	7.16 (7.19)	33.60 (33.31)
4e	C_6H_5CHOH	91[c]	114-115[g]	$C_9H_9N_3O$	-	-	-
4f	$4\text{-}CH_3C_6H_4CHOH$	89[c]	121-122	$C_{10}H_{11}N_3O$	63.15 (63.48)	5.81 (5.86)	22.46 (22.21)
4g	C_6H_5NHCO	98[c]	229-230[h]	$C_9H_8N_3O$	-	-	-
4h	$(C_6H_5)_2COH$	87[d]	226-227[f]	$C_{13}H_{13}N_3O$	-	-	-
4i	C_6H_5S	57[d]	79-81	$C_8H_7N_3S$	54.21 (54.22)	4.03 (3.98)	23.80 (23.71)
4j	$C_6H_5CH_2S$	54[d]	70-71	$C_9H_9N_3S$	56.64 (56.52)	4.70 (4.74)	21.57 (21.97)

[a] Isolated yield. [b] Uncorrected. [c] Deprotected by using $NaBH_4$ in refluxing ethanol. [d] Isolated as deprotected product after workup in lithiation reaction. [e] Lit.[4a] mp. 94-95°C. [f] Lit.[10] mp. 226-227°C. [g] Lit.[24] mp. 116-117°C. [h] Lit.[25] mp. 230-231.5°C.

Table 5. ^{1}H-NMR Chemical Shifts (δ) for 3(5)-Substituted-1,2,4-triazoles 4 (ppm)

Compd	Triazole H-3(H-5)	Triazole NH	3(5)-Substituent protons		
4a	7.98 (s)[a]	6.62 (bs)	5.32 (bs, 1 H, OH)	1.18-2.12 (m, 10 H)	
4c	8.05 (s)[a]	6.03 (bs)	2.35 (s, 3 H, CH_3)		
4d	7.75 (s)[a]	.[c]	1.39 (s, 9 H, CH_3)	7.30 (bs, 1 H, NH)	
4e	8.07 (s)[a]	.[c]	5.86 (s, 1 H, CH)	6.23 (bs, 1 H, OH)	7.25-7.45 (m, 5 H)
4f	8.24 (s)[a]	6.88 (bs)	2.54 (s, 3 H, CH_3)	6.07 (s, 1 H, CH)	6.45 (bs, 1 H, OH)
			7.40 (d, J = 8 Hz, 2 H)	7.57 (d, J = 8 Hz, 2 H)	
4g	8.63 (s)[a]	.[c]	7.13-7.38 (m, 3 H)	7.86 (m, 2 H)	10.52 (s, 1 H, amide NH)
4h	7.98 (s)[a]	7.08 (bs)	2.58 (s, 1 H, OH)	7.18-7.58 (m, 10 H)	
4i	8.52 (s)[a]	.[c]	7.19-7.58 (m, 5 H)		
4j	8.10 (s)[b]	.[c]	4.13 (s, 2 H, CH_2)	7.15-7.38 (m, 5 H)	

[a] DMSO-d6 as solvent and TMS as internal standard. [b] $CDCl_3$ as solvent and TMS as internal standard. [c] NH missing.

As Table 4 shows, the yields of the deprotected products are high and the reaction conditions are mild. A variety of substituents, such as alkyl, hydroxyalkyl and carbamoyl, survive intact under these conditions. The compounds listed in Table 4 are characterized by their analyses, and by ^{1}H (Table 5) and ^{13}C (Table 6) nmr spectra.

In summary, the present method provides a novel route to the synthesis of 3(5)-substituted 1,2,4-triazoles via a three-step sequence. It appears that, as a protecting group for the N of 1,2,4-triazole, the aminal group is superior to those previously available in terms of ease of introduction and of removal.

Table 6. ^{13}C-NMR Chemical Shifts (δ) for 3(5)-Substituted-1,2,4-triazoles 4 (ppm)

Compound	Triazole		3(5)-Substituent					
	C-3	C-5						
4a	148.8	164.1[a]	21.4	25.1	36.8	68.8		
4c	148.1	154.4[a]	12.1					
4d	150.9	157.2[a]	28.8	49.9	162.6			
4e	147.9	160.7[a]	68.7	126.6	127.4	128.1	142.5	
4f	148.7	160.8[a]	20.7	68.5	126.5	128.6	136.5	139.5
4g	146.9	154.4[a]	120.5	124.1	128.7	138.3	157.0	
4h	148.4	162.2[a]	76.8	126.8	127.1	127.6	145.8	
4i	146.7	154.9[a]	127.3	129.3	130.1	132.7		
4j	146.7	156.2[b]	37.2	127.4	128.6	136.5		

[a] DMSO-d6 as solvent and standard. [b] $CDCl_3$ as solvent and standard.

Experimental Section

Melting points were measured with a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. ^{1}H NMR (200 MHz) spectra were recorded on a Varian XL 200 (FT mode) spectrometer using TMS as internal standard. ^{13}C NMR (50 MHz) spectra were recorded on a Varian XL 200 (FT mode) spectrometer using DMSO-d_6 or $CDCl_3$ as internal standard. Tetrahydrofuran and diethyl ether were predried over 4A molecular sieves and distilled from sodium/benzophenone before use. Commercial 1,2,4-triazole (Aldrich) and pyrrolidine (Aldrich) were used without purification. n-Butyllithium (Aldrich) was used without purification. Electrophiles were purified by standard methods before use.

Preparation of 1-(1-Pyrrolidinomethyl)-1,2,4-triazole 2: 1,2,4-Triazole (7.81 g, 0.11 mol), pyrrolidine (8.5 g, 0.12 mol), and formaldehyde (3.6 g, 10 ml, 0.12 mol; 37% aqueous solution) were mixed and dissolved in 50 ml of ethanol. The mixture was refluxed for 4 hr and the solvent was removed under vacuum. The residue was diluted with water and extracted with chloroform (3 x 25 ml). After drying with Na_2SO_4 the solvent was concentrated and the resulting oil was further distilled under vacuum (98-100°C/1.2 torr) to give a pure oil. Yield: 13.72 g (82%). ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 1H, C_5-H), 7.98 (s, 1H, C_3-H), 5.19 (s, 2H, CH_2), 2.77 (m, 4H), 1.78 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 150.9 (C-3), 143.0 (C-5), 65.9 ($\underline{C}H_2$), 49.2, 23.3. MS (HR) calculated for $C_7H_{11}N_4$ (M^+ - 1) 151.0984, found 151.0989.

Lithiation and Electrophilic Additions of 1-(1-Pyrrolidinomethyl) -1,2,4-triazoles 2. General Procedure for the preparation of 3: 1-(1-Pyrrolidinomethyl)-1,2,4-triazole **2** (1.52 g, 10 mmol) was dissolved in 20 ml of tetrahydrofuran, and the solution was cooled to -78°C with stirring under argon. n-Butyllithium (4.2 ml, 11 mmol, 2.5 M in hexane) was added slowly via syringe. A heavy precipitate was formed indicating the formation of the lithium salt. The mixture was stirred at -78°C for 30 min and then warmed up to -25°C for 30 min. After cooling down to -78°C, the electrophile (11 mmol) in 2 ml of THF was added dropwise. The reaction mixture was stirred at -78°C for 3 hr and then warmed up to room temperature overnight. Water (20 ml) was added, and the mixture was then extracted with chloroform (4 x 25 ml). The combined extracts were dried over Na_2SO_4 and the solvent was then evaporated to give the crude product. The crude product could be purified by recrystallization if solid. Physical data of products, and yields are given in Table 1.

Deprotection of 3-Substituted 1-(1-Pyrrolidinomethyl)-1,2,4-triazole. General Procedure. A 3-substituted 1-(1-pyrrolidinomethyl) 1,2,4-triazole (0.5 g) was added to the ethanol solution (10 ml) of $NaBH_4$ (1 equiv. mole) and the mixture was refluxed for 2-3 hr. Following which, the ethanol solution was evaporated under vacuum and the residue was dissolved in water. The water solution was continuously extracted with ethyl acetate in a continuous liquid-liquid extraction apparatus. The combined extracts were dried with Na_2SO_4 and then evaporated to give the crude product. The crude product could be further purified by recrystallization. The physical data of products, and yields are listed in Table 4.

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