Pakistan J. Sci. Ind. Res., Vol. 27, No. 2, April 1984

SYNTHESIS OF SOME NEW MONO– AND DISUBSTITUTED N-TOSYL– OR N-PHTHALYL-AMINOACYL 3-AMINO-1, 2, 4-TRIAZOLE DERIVATIVES

A.M. El-Naggar, F.S.M. Ahmed, I.M. Ismail
and
H.M. Abd El-Bary

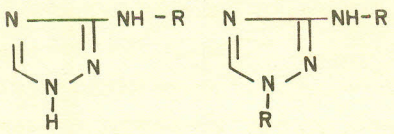
Chemistry Department, Faculty of Science,
Al-Azhar University,
Nasr-City, Cairo, Egypt

(Received February 1, 1981)

N-Pht-Gly-3-amino-1, 2, 4-triazole (II) and the corresponding N-Pht-DL-Phe-, N-Tos-B-Ala- and N-Tos-DL-Ala-derivatives (III-V) and 3-(N-Pht-B-Ala) amino-N-(N-Pht-B-Ala)-1, 2, 4-triazole (VI) and the corresponding N-Pht-L-Val-, N-Pht-L-Leu-, N-Tos-Gly-, N-Tos-L-Ala- and N-Tos-L-Val-derivatives (VII-XI) have been synthesized by the reaction of N-tosyl- or N-phthalyl-amino acid with 3-amino-1, 2, 4-triazole (I) in THF or DMF using the DCCD method.

INTRODUCTION

It is well established that several substituted 3-amino-1, 2, 4-triazole derivatives possess different pharmacological applications [1, 2]. Recently, we have reported on the synthesis of N-Tos- and N-Pht-aminoacyl derivatives of several amino-heterocyclic compounds and some were found to possess interesting biological activities [3-6]. As a continuation of this work the synthesis of N-Pht-or N-Tos-aminoacyl-3-amino-1, 2, 4-triazoles (II-V) and 3-(N-Tos- or N-Pht-aminoacyl)- amino-N-(N-Tos- or N-Pht-aminoacyl)-1, 2, 4-triazole derivatives (VI-XI) and the studies of their antimicrobial activities are described in this investigation.



(Compounds type A) (Compounds type B)

N-Tos- or N-Pht-aminoacyl-3-amino-1, 2, 4-triazoles (II-V) were readily prepared using the carbodiimide method. Coupling of N-Tos-B-Ala- or (N-Tos-DL-Ala-) or N-Pht-Gly- (or N-Pht-DL-Phe-), 0.028 mole, with 3-amino-1, 2, 4-triazole [7] (0.028 mole) in THF using DCC procedure afforded the desired aminoacyl derivatives (II-V). Structures of compounds (II-V) were confirmed as mono-3-N substituted-1, 2, 4-triazole derivatives on the basis of elemental analyses, chromatographic studies, IR and UV data.

The IR spectrum of N-Tos-DL-Ala-3-amino-1, 2, 4-triazole (V) in KBr showed characteristic bands at: 3380, 3300, 3040 (NH, SO_2NH, N); 2960, 2840, 1740, 1480 (1, 2, 4-triazole nucleus); 1790, 1720 ($\gtrless$C=O); 1650, 1550, 1360 (amide I, II and III); 1690, 1440, 1260, 1140, 1080, 960 and 740 cm^{-1} (benzene, aminoacyl and 1, 2, 4-triazole residues), thereby confirming the structure of (V). The UV spectrum of (V) in ethanol showed the expected absorption maxima of 1, 2, 4-triazole residue at λ_{max} (log ϵ): 210 nm (3.98) and 249 nm (4.26). The IR and UV spectra of other compounds (II-V) showed analogous peaks confirming their structures.

Previously, Davidson and Dhami [8], published their work on the elucidation of the structure of some benzoyl derivatives of 3-amino-5-phenyl-1, 2, 4-triazoles using UV and IR spectroscopy. Recently, Dvortsak and Reiter [9], reported the uses of ^{1}H- and ^{13}C-NMR spectroscopy for determination of the position of substituents and structure of some acylated 1, 2, 4-triazoles.

^{1}H-NMR data for compound II- (A): 3.46 (S, 2H, CH_2); 7.50 – 8.11 (S, 5H, benzene and triazole protons); 5.83 (S, 2H, NH_2 or 2NH). Compounds III-V gave NMR data containing analogous peaks confirming their structures. Moreover, both the N-phthalyl- and N-tosyl substituted triazole derivatives (II-V) were found to be soluble

in lN-sodium hydroxide solution at 45°. The NMR data and the solubility of these compounds in lN-NaOH are in good agreement with the results published by Davidson [8] and Dvortsak [9] concerning determination of the structures of other similar substituted 1, 2, 4-triazoles, and therefore confirming the structures of II-V.

The reaction of N-Pht-Gly- or (N-Pht-DL-Phe- or N-Tos-B-Ala- or N-Tos-DL-Ala-) with 3-amino-1, 2, 4-traizole and DCCD (2:1:2 moles) using THF or DMF as solvent gave mainly the monosubstituted (II-V) products, even after boiling for several hours. The products (II-V) were obtained in well crystalline form in 48-68% yields. Isolation of the disubstituted (3-NH_2 and 1-NH) derivatives were unsuccessful.

However, the reactions of N-Pht-B-Ala- or (N-Pht-L-Val- or N-Pht-L-Leu- or N-Tos-Gly- or N-Tos-L-Ala- or N-Tos-L-Val-) with 3-amino-1, 2, 4-triazole (2:1 moles) in THF or DMF using the DCC procedure afforded the disubstituted (VI-XI) derivatives. The products (VI-XI) were easily isolated, purified by repeated recrystallizations and obtained in 52 – 76% yields. Compounds (VI-XI) were chromatographically homogeneous and their structures were assigned on the basis of elemental analysis, IR and UV data. Isolation of the monosubstituted derivatives during preparation of (VI-XI) were fruitless.

The IR spectrum of 3-(N-Pht-L-Leu) amino-N-(N-Pht-L-Leu)-1, 2, 4-triazole (VIII) in KBr showed characteristic bands at: 3360, 3040, (NH, N); 2960, 2840, 1740, 1490 (1, 2, 4-triazole); 1790, 1720 ($\gtrless$C=O); 1660, 1560, 1380 (amide I, II and III); 2820, 1710, 1440, 1160, 1060, 940 and 720 cm^{-1} (benzene, aminoacyl and 1, 2, 4-traizole residues), thereby confirming the structure of (VIII). The UV spectrum of (VIII) in ethanol revealed the expected absorption maxima of lN- and 3-N substituted-1, 2, 4-triazole moiety at λ_{max} (log ϵ) 210 nm (3.88). Analogous peaks were observed in the IR and UV spectra of compounds (VI-XI) concordant with their structures.

The present investigation reveals that the steric effect of some N-protecting groups, constitution and optical properties of the amino acid and the solvent used play an impotant role and should be taken into consideration during synthesis of the mono- and disubstituted 1, 2, 4-triazole derivatives.

All the synthesized derivatives (II-XI) were found to be inactive against *Bacillus subtilis, Bacillus mycoids, Bacillus cereus, Escherichia coli, Salmonella typhosa* and *Pencicillum chrysogeneum.* Other pharmacological studies are in progress.

EXPERIMENTAL

All melting points are uncorrected. Paper chromatography was performed on Whatman No. 1 paper, in the system R_f: *n*-butanol-pyridine acetic acid- water (15 : 10 : 3 : 12) [10]. Paper electrophoresis was carried out on Whatman No. 1 paper by the method of vertical high voltage electrophoresis with E-pyridine-acetate buffer (pH 5.6), at 1000 V for 2 hr. Benzidine and ninhydrin were used for development. Optical rotations are equilibrium values and were measured in DMF (c, 0.6) at 20°.

The IR spectra were taken in KBr on a Unicam SP 1200 instrument and the UV spectra were taken in ethanol on a Unicam SP 8000 spectrophotometer. NMR spectra in DMSO-d_6 were run on a Varian-T-60 A instrument (chemical shift in (δ), ppm) using TMS as the internal standard.

3-Amino-1, 2, 4-triazole (I)- was prepared as described earlier [2, 7].

General Procedure for Synthesis of N-Pht- or N-Tos-aminoacyl-3-amino-1, 2, 4-triazoles (II-V). N-Pht- or N-Tos-amino acid (0.028 mole) and 3-amino-1, 2, 4-triazole (0.028 mole) were dissolved in THF (250 ml). The mixture was cooled to 0-5°, dicyclohexylcarbodiimide (5.4 g) added and the mixture stirred 4 hr. at 0° and left for 24 hr. at room temperature. The dicyclohexylurea was filtered off and few drops of gl. acetic acid added and the mixture left for 2 hr. at 0° and then refiltered again. The filtrate was evaporated in vacuo and the residual solid recrystallized from ethanol or ethanol – water (1:1) mixture. The products (II-V) were soluble in THF, dioxane, DMF and alcohols and insoluble in water, ether and pet. ether. The materials were chromatographically homogeneous when developed with benzidine or iodine solution and showed negative ninhydrin reactions. E = zero for all compounds indicating the high purity of the synthesized products (cf. Table 1, compounds II-V).

General Procedure for Synthesis of 3-(N-Tos- or N-Pht-aminoacyl)- amino-N-(N-Tos- or N-Pht-aminoacyl)-1, 2, 4-triazoles (VI-XI). N-Tos- or N-Pht-amino acid (0.04 mole) and 3-amino-1, 2, 4-triazole (I, 0.02 mole) were dissolved in THF (250 ml) or DMF (250 ml). The mixture was cooled to 0°, dicyclohexylcarbodiimide (8.2 g) added and the mixture allowed to proceed as described for (II-V). The

Table 1. Physical data of various mono- and disubtituted 3-amino-1, 2, 4-triazole derivatives (II-XI).

Compd. No. (Type)	R–	Yield (%)	m.p. C°	R_f	Mol. formula	N (%) *) Calc.	N (%) *) Found
II-(A)	Pht-Gly-	58	174–176	0.95	$C_{12}H_9N_5O_3$	25.83	25.85
III-(A)	Pht-DL-Phe-	68	195–197	0.61	$C_{19}H_{15}N_5O_3$	19.39	19.41
IV-(A)	Tos-β-Ala-	57	229–231	0.73	$C_{12}H_{15}N_5O_3S$	22.65	22.74
V-(A)	Tos-DL-Ala-	66	252–254	0.76	$C_{12}H_{15}N_5O_3S$		
VI-(B)	Pht-β-Ala-	59	160–162	0.62	$C_{24}H_{18}N_6O_6$	17.28	17.39
VII-(B)	Pht-L-Val-**)	73	155–157	0.61	$C_{28}H_{26}N_6O_6$	15.49	15.58
VIII-(B)	Pht-L-Leu-	52	180–182	0.84	$C_{30}H_{30}N_6O_6$	14.73	14.86
IX-(B)	Tos-Gly-	63	224–226	0.65	$C_{20}H_{22}N_6O_6S_2$	16.54	16.70
X-(B)	Tos-L-Ala-	71	181–183	0.67	$C_{22}H_{26}N_6O_6S_2$	15.73	17.75
XI-(B)	Tos-L-Val-	76	120–122	0.58	$C_{26}H_{34}N_6O_6S_2$	14.23	14.35

*) All the compounds gave satisfactory C and H analyses.

**) $[\alpha]_D^{20}$, (c = 0.6 DMF) for compounds (VII) = −22.5; (VIII) = −30.6, (X) = −12; and (XI) = −14.5

crude products were recrystallized from ethanol-water. All the products (VI-XI) were chromatographically homogeneous (detection with benzidine), and showed negative ninhydrin reactions. E = zero for all compounds, (cf. Table 1, compounds VI-XI).

REFERENCES

1. D.H. Hey, *Organic Chemistry, Heterocyclic Coumpounds,* K. Schofield (Butterworth & Co., London – Boston, 1975), p. 51.
2. A. Albert, *Heterocyclic Chemistry* (The Athlone Press, University of London, 1968), p. 249.
3. A.M. El-Naggar, F.S.M. Ahmed and M.F. Badie, J. Heterocyclic Chem., **18**, 91 (1981).
4. A.M. El-Naggar, I.M. Ismail and A.M. Gommaa, Indian J. Chem., **15B**, 850 (1970).
5. M.H.A. El-Gamal, A.M. El-Naggar, B.A.H. El-Tawil and F.S.M. Ahmed, Acta. Chim. Hung. (Budapest), **91**, 441 (1976).
6. M.H.A. El-Gamal, A.M. El-Naggar, B.A.H. El-Tawil and A.M. Abd El-Salam, Roczniki Chemii, **50**, 765 (1976).
7. T. Oshima, S. Hata, H. Takamatsu, M. Okuda and M. Yokota, Jap. Pat., 7208 802, (1972); Chem. Abstr., **76**, 153 793 (1972).
8. J.S. Davidson and S.S. Dhami, Chemistry and Industry, 2, 92 (1978).
9. P. Dvortsak, J. Reiter and L. Pongo, 8th International Congress of Heterocyclic Chemistry (Graz, Austria, 1981), p. 459.
10. A.M. El-Naggar, Indian J. Chem., **9**, 1326 (1971).