http://www.e-journals.net

ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
2011, **8(3),** 1180-1185

Synthesis of *N*-(5-(Substitutedphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazol-4-amine from 4-Amino-4*H*-1,2,4-triazole

ASHVIN D. PANCHAL and PRAVIN M. PATEL*

Industrial Chemistry Department, V.P. & R.P.T.P. Science College
Vallabh Vidyangar- 388120. Anand, Gujarat. India
drpravinpatel@rediffmail.com

Received 5 October 2010; Accepted 16 December 2010

Abstract: *N*-(4*H*-1,2,4-Triazol-4-yl)acetamide (**2**) were prepared by reaction of 4-amino-4*H*-1,2,4-triazole (**1**) with acetyl chloride in dry benzene. It has been reacted with various aromatic aldehyde to afford 3-(substitutedphenyl)-*N*-(4*H*-1,2,4-triazol-4-yl)acrylamide (**3a-e**). The synthesis of *N*-(5-substitutedphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazol-4-amine (**4a-e**) is achieved by the cyclisation of **3a-e** with hydrazine hydrate in ethanol. The structures of synthesized compounds were characterized by ^{1}H NMR and IR spectroscopic studies. The purity of the compounds was checked by thin layer chromatography.

Keywords: Triazole, Pyrazoline, *N*-(5-(Substitutedphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazol-4-amine, 3-(Substitutedphenyl)-N-(4*H*-1,2,4-triazol-4-yl)acrylamide.

Introduction

In the last few decades, the chemistry of 1,2,4-triazoles has received considerable attention owing to their synthetic and effective biological importance. 1,2,4-Triazole moieties have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatories, CNS stimulants, sedatives, antianxiety compounds, antimicrobial agents[1-3] and antimycotic ones such as fluconazole, intraconazole, voriconazole[4,5]. There are marketed drugs containing the 1,2,4-triazole group, *e.g.,* triazolam[6], Alprazolam[7], Etizolam[8] and Furacylin[9]. In addition to these important biological applications, 1,2,4-triazoles are also of great utility in preparative organic chemistry, for example, in the presence of various reagents, undergo different types of reactions to yield other heterocyclic compounds.

Pyrazolines and their derivatives have been found to possess a broad spectrum of biological activities such as antibacterial[10–12], antidepressant[13] anticonvulsant[14–16] antihypertensive[17] antioxidant[18] antitumor[19] and anticancer activities[20,21]. Recently these classes of compounds are reported to possess potential antiviral activity against flavivirus[22]

and HIV[23]. Our literature survey revealed that these classes of compounds are yet to be explored with 1,2,4-triazole ring system. In this study, only the HY-ALI feature associated with 'B' ring of the substituted pyrazoline moiety was changed by keeping the basic skeleton intact.

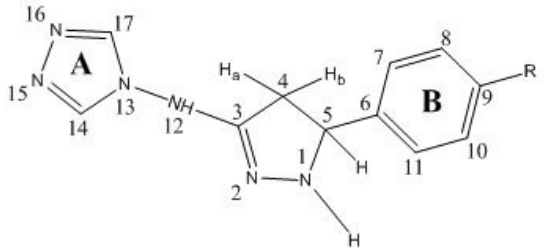


Figure 1

Experimental

Melting points were determined in open capillary tubes and are uncorrected. All the chemicals and solvents used were of laboratory grade and solvents were purified by suitable methods. IR (Infrared spectrum) (KBr, cm^{-1}) were recorded on a Shimadzu-8400 FT-IR spectrometer using KBr disc, ^1H NMR spectra were recorded on a brucker avance II 400 NMR spectrometer using TMS as an internal standard (chemical shift in δ, ppm) in $CDCl_3$. The homogeneity of the products was checked by TLC using silica gel GF_{254} (E.Merck) and the eluent system was a mixture of acetone - pet.ether in 2:8 proportions.

General procedure for the preparation of N-(4H-1,2,4-triazol-4-yl)acetamide ***(2)***

To a solution of 4-amino-4*H*-1,2,4-triazole (0.01 mol) in dry benzene (50 mL), acetylchloride (0.01 mol) was added drop by drop at 0-5 °C. The reaction mixture was stirred for 1 h and kept overnight. The reaction mixture was distilled off and then poured onto ice. The solid thus obtained was recrystallized from suitable solvent. Physical, analytical data are given in Table 1.

Table 1. Physical data of synthesized compounds **2, 3a-e** and **4a-e**

Compound	R	M.P., °C	Yield, %	Mol. Formula	Mol. Wt.	Solvent used for recryllization
2	-	155	84	$C_4H_6N_4O$	126	Methanol
3a	4-Cl	159	74	$C_{11}H_9ClN_4O$	248	Methanol
3b	4-N(CH_3)	186	70	$C_{13}H_{15}N_5O$	257	Ethanol
3c	Naphthalene	225	69	$C_{15}H_{12}N_4O$	264	Acetone
3d	3-OCH_3	126	72	$C_{12}H_{12}N_4O_2$	244	Methanol
3e	2-OH	196	65	$C_{11}H_{10}N_4O_2$	230	Ethanol
4a	4-Cl	198	60	$C_{11}H_{11}ClN_6$	262	Ethanol
4b	4-N(CH_3)	254	50	$C_{13}H_{17}N_7$	271	Ethanol
4c	Naphthalene	>300	55	$C_{15}H_{14}N_6$	278	Ethanol-Water
4d	3-OCH_3	162	58	$C_{12}H_{14}N_6O$	258	Ethanol
4e	2-OH	214	54	$C_{11}H_{12}N_6O$	244	Methanol-Water

General procedure for the preparation of 3-(substitutedphenyl)-N-(4H-1,2,4-triazol-4-yl)acrylamide ***(3a–3e)***

A solution of *N*-(4*H*-1,2,4-triazol-4-yl)acetamide (0.01 mol) in absolute ethanol (50 mL) was refluxed with various aromatic aldehydes in the presence of 2% NaOH (5 mL) for 10 h,

concentrated, cooled and poured onto ice. The solids thus obtained were recrystallized from appropriate solvents. Physical, analytical and spectroscopic data of compounds are given below.

*3-(4-Chlorophenyl)-N-(4H-1,2,4-triazol-4-yl)acrylamide**(3a)***

White crystals, yield 74%, m.p. 159 ^{o}C; TLC (Acetone: Toluene, 2:8). IR: (KBr, cm^{-1}) 3426 (N-H), 3123 (Ar C-H stretch), 2925 and 2852 (C-H stretch), 1691 (NH-C=O), 1653 (CH=CH of –Carbonyl-CH=CH-), 1595 (C=N in triazole ring), 1513 (C=C of aromatic ring), 762 (C-Cl). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.31 (ss, 1H, N-H), 7.40-7.38 (d, 1H, -CO-CH=), 7.99-7.97 (d, 1H, =CH-Ar), 7.49-7.47 (d, 2H, Ar-H), 7.84-7.81 (d, 2H, Ar-H), 8.80 (ss, 2H, -CH=N in triazole ring).

*General procedure for the preparation of N-(5-(substitutedphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4H-1,2,4-triazol-4-amine**(4a-e)***

To a solution of compound (**3a-3e**) (0.02 mol) and 99% hydrazine hydrate (0.04 mol) in absolute ethanol and few drops of hydrochloric acid was added. The reaction mixtures were refluxed for 8-10 h, distilled in vacuum and cooled. The separated solids were filtered, washed with ether and recrystallized from appropriate solvents. Physical, analytical and spectroscopic data of compounds (**4a-4e**) are as follows.

*N-(5-(4-Chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4H-1,2,4-triazol-4-amine**(4a)***

Yellowish crystals, yield 60%, m.p. 198 ^{o}C; TLC (Acetone: Pet.ether, (2:8). IR: (KBr, cm^{-1}) 3110 (N–H), 3070 (Ar CH stretch), 2985 and 2930 (C-H stretch), 1630 (C=N) in pyrazoline ring, 1580 (N-N) in pyrazoline ring, 1380 (C–N). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.45 (d, 2H, Ar–H), 7.79 (d, 2H, Ar-H), (s, 1H, -NH- missing), 7.26 (s, 1H, NH in pyrazoline ring), 7.78-7.76 (dd, 2H, CH_2 in pyrazoline ring), 8.60 (s, 2H, CH=N in triazole ring).

*N-(5-(4-(Dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4H-1,2,4-triazol-4-amine **(4b)***

Yellowish crystals, yield 50%, m.p. 254 ^{o}C; TLC (Acetone: Pet.ether, (2:8). IR: (KBr, cm^{-1}) 3410 (N–H), 3060 (Ar CH stretch), 2915 and 2840 (C-H stretch), 1610 (C=N) in pyrazoline ring, 1520 (N-N) in pyrazoline ring, 1360 (C–N). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.69 (d, 2H, Ar–H), 7.71 (d, 2H, Ar–H), (s, 1H, -NH- missing), 7.25 (s, 1H, NH in pyrazoline ring), 6.72-6.70 (dd, 2H, CH_2 in pyrazoline ring), 8.58 (s, 2H, CH=N in triazole ring), 3.02 (s, 6H, N-$(CH_3)_2$).

*N-(5-(Naphthalen-1-yl)-4,5-dihydro-1H-pyrazol-3-yl)-4H-1,2,4-triazol-4-amine**(4c)***

Yellowish crystals, yield 55%, m.p. >300 ^{o}C; TLC (Acetone: Pet.ether, (2:8). IR: (KBr, cm^{-1}) 3420 (N–H), 3080 (Ar CH stretch), 2940 and 2860 (C-H stretch), 1580 (C=N) in pyrazoline ring, 1510 (N-N) in pyrazoline ring, 1325 (C–N). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.91-7.40 (m, 7H, Ar–H of Naphthalene), (s, 1H, -NH- missing), 7.28 (s, 1H, NH in pyrazoline ring), 7.73-7.71 (dd, 2H, CH_2 in pyrazoline ring), 9.68 (s, 2H, CH=N in triazole ring).

*N-(5-(3-Methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4H-1,2,4-triazol-4-amine **(4d)***

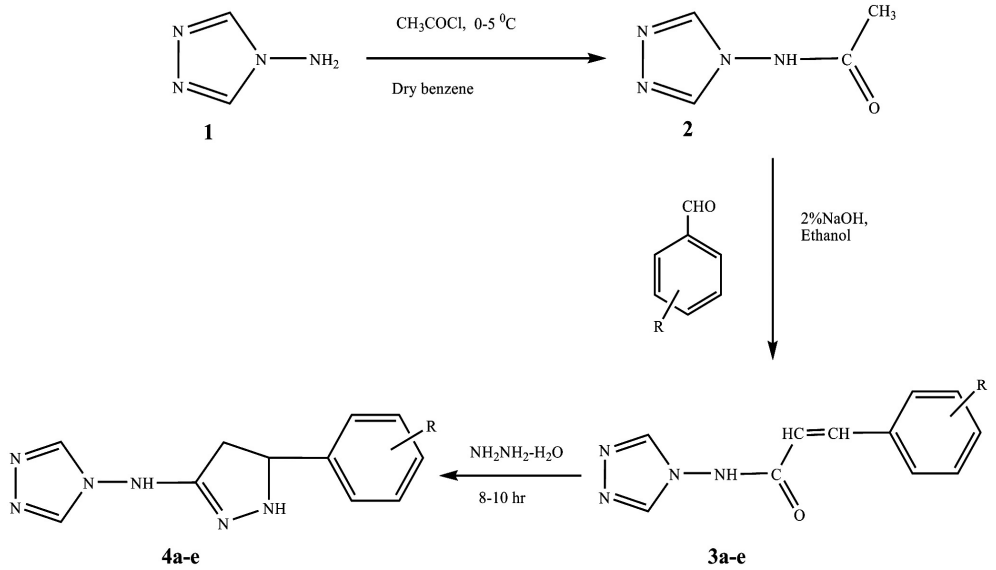
Greenish crystals, yield 58%, m.p. 162 ^{o}C; TLC (Acetone: Pet.ether, (2:8). IR: (KBr, cm^{-1}) 3140 (N–H), 3020 (Ar CH stretch), 2910 and 2830 (C-H stretch), 1600 (C=N) in pyrazoline ring, 1515 (N-N) in pyrazoline ring, 1300 (C–N). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.97-6.94 (d, 2H, Ar–H), 7.77 (d, 1H, Ar-H), 7.80 (d, 1H, Ar-H), (s, 1H, -NH- missing), 7.25 (s, 1H, NH in pyrazoline ring), 7.78-7.79 (dd, 2H, CH_2 in pyrazoline ring), 8.62 (s, 2H, CH=N in triazole ring), 3.85 (s, 3H, Ar-OCH_3).

*2-(3-(4H-1,2,4-triazol-4-ylamino)-4,5-dihydro-1H-pyrazol-5-yl)phenol(**4e**)*

Shiny greenish crystals, yield 54%, m.p. 214 ^{o}C; TLC (Acetone: Pet.ether, (2:8). IR: (KBr, cm^{-1}) 3440 (N–H), 3010 (Ar CH stretch), 2970 and 2860 (C-H stretch), 1620 (C=N) in pyrazoline ring, 1570 (N-N) in pyrazoline ring, 1360 (C–N), 1260, 1040 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.41-6.95 (m, 4H, Ar–H), (s, 1H, -NH- missing), 7.30 (s, 1H, NH in pyrazoline ring), 7.34-7.32 (dd, 2H, CH_2 in pyrazoline ring), 8.71 (s, 2H, CH=N in triazole ring), 11.38 (s, 1H, Ar-OH).

Results and Discussion

N-(5-(Substitutedphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazol-4-amine **(4a–e)** were synthesized according to the method shown in Scheme 1. In the first step, synthesis of *N*-(4*H*-1,2,4-triazol-4-yl)acetamide were carried out by the acetylation of 4-amino-1,2,4-triazole by acetyl chloride and products were purified by recrystallization from suitable solvent (75–85% yield). Then in second step, synthesis of chalcone carried out by the reaction of *N*-(4*H*-1,2,4-triazol-4-yl)acetamide and different aromatic aldehyde with 2% NaOH in absolute ethanol and the products were purified by recrystallization from suitable solvents. In last step, synthesis of pyrazoline derivatives by undergoes cyclization of chalcones with hydrazine hydrate in the presence of few drops of HCl in absolute ethanol.



Scheme 1. Synthesis of *N*-(5-(substituted phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazol-4-amine (**4a-e)**

The yellow contour represents the hydrophobic aliphatic feature (HY-ALI), the yellow contour at ring represents ring aromatic feature (AR), the green contour represents hydrogen bond donor feature (HBD) and the red contour represents Hydrogen bond acceptor (HBA). Figure 2 shows the mapping of pyrazoline for all the pharmacophoric features except PI (positive ionisable). On the basis of pharmacophore mapping, we hypothesized that this type of substituted pyrazolines may show potential Pharmacological and biological activity.

Factors such as the structure and position of the substituents have profoundly influenced the rate of the reaction. The generally accepted interpretation of this reaction, involves the initial formation of an aryl hydrazone with subsequent nucleophilic attack of nitrogen upon

the carbon-carbon double bond at β position of chalcones. Hence the electropositive nature of β carbon may control the overall rate of the reaction. The electropositive nature of β carbon is controlled by the aromatic ring directly connected to it. Halogens being electron withdrawing in nature significantly increase the positive character of β carbon lead to faster reaction while electron donating alkyl and alkoxy groups contributed for slower reaction.

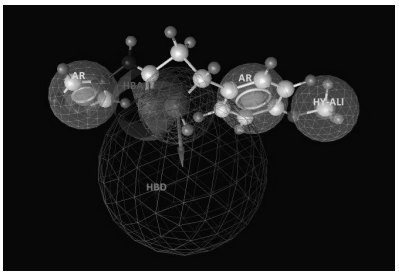


Figure 2. Pharmacophore mapping of pyrazoline derivative

Structures of compounds **4a–e** were confirmed by IR and ^{1}H NMR spectroscopic techniques. All of the pyrazolines possesses similar basic skeletal structure. Proton NMR signals were assigned by comparing the spectra of the products (**4a–e**) with their corresponding chalcones. Signals around δ value 7.76 and 7.78 ppm recorded as doublet of doublet (dd) were assigned to 4-H_a and 4-H_b protons of pyrazoline ring. The *J* values were calculated for above signals and found to be around 8 Hz. 5-*H* proton (δ around 7.44-7.41 ppm) of pyrazoline ring showed a multiplet pattern of *J* value around 13 Hz and most likely interacting with 4-H_a and 4-H_b protons.

Conclusion

This study describes the synthesis of novel substituted pyrazoline derivatives and their characterization by IR and ^{1}H NMR spectroscopic techniques successfully.

Acknowledgment

The author's wishes to express their thanks to, Principal, V.P. & R.P.T.P. Science College, the Head and Staff of Industrial Chemistry Department for providing laboratory facility.

References

1. Heindel N D and Reid J R, *J Heterocycl Chem*., 1980, **17,** 1087.
2. Holla B S, Kalluraya B, Sridhar K R, Drake E, Thomas L M, Bhandary K K and Levine M J, *Eur J Med Chem.,* 1994, **29,** 301-308.
3. Mathew V, Keshavayya J, Vidya V P, Acharya and Reddy B M, *Eur J Med Chem.,* 2006, **41,** 1048.
4. The Merck Index, *Merck Co. Inc.*, Twelfth Ed., USA, 1996.
5. Haber J, Present Status and Perspectives on Antimycoties with Systematic Effects, *Cas Lek Cesk.,* 2001, **140,** 596.
6. Brucato A, Coppola A, Gianguzza S and Provenzano P M, *Boll Soc Ital Biol Sper.,* 1978, **54,** 1051.
7. Coffen D L and Fryer R I, *U.S. Patent* 1974, **3**, 849, 434; *Chem Abstr.,* 1975, **82,** 73044v.
8. Shiroki M, Tahara T and Araki K, *Jap Patent,* 75100096, 1975, *Chem Abstr.,* 1976, **84,** 59588k.
9. Povelitsa F D and Gural A G, *Antibiotiki Moscow,* 1973, **18,** 71; *Chem Abstr.,* 1973, **78,** 93044.

10. Ali M A, Shaharyar M, Siddiqui A A, Sriram D, Yogeeswari P and Clercq E D, *Acta Pol Pharma Drug Res.,* 2007, **63,** 435-439.
11. Shaharyar M, Siddiqui A A and Ali M A, *Bioorg Med Chem Lett.,* 2006, **16,** 4571-4554.
12. Chimenti F, Bizzarri B, Manna F, Bolasco A, Secci D, Chimenti P, Granese A, Rivanera D, Lilli D, Scaltritoc M M and Brenciaglia M I, *Bioorg Med Chem Lett.,* 2005, **15,** 603-607.
13. Prasad Y R, Rao A L, Prasoona K, Murali K and Kumar P R, *Bioorg Med Chem Lett.,* 2005, **15,** 5030-5034.
14. Parmar S S, Pandey B R, Dwivedi C and Harbinson R D, *J Pharm Sci.,* 1974, **63,** 1152-1155.
15. Soni N, Pande K, Kalsi R, Gupta T K, Parmar S S and Barthwal J P, *Res Commun Chem Pathol Pharmacol*., 1987, **56,** 129-132.
16. Batulin Y M, *Farmakol Toksikol.,* 1968, **31,** 533.
17. Turan-Zitouni G, Chevallet P, Kilic F S and Erol K, *Eur J Med Chem*., 2000, **35,** 635.
18. Jeong T-S, Kim K S, Kim J-R, Cho K- H Lee S and Lee W S, *Bioorg Med Chem Lett.,* 2004, **14,** 2719-2723.
19. Johnson M, Brent Younglove B, Lee L, LeBlanc R, Holt Jr H, Hills P, Mackay H, Brown T, Mooberry S L and Lee M, *Bioorg Med Chem Lett.,* 2007, **17,** 5897-5901.
20. Manna F, Chimenti F, Fioravanti R, Bolasco A, Secci D, Chimenti P, Ferlini C and Scambia G, *Bioorg Med Chem Lett.,* 2005, **15,** 4632-4635.
21. Roecker A J, Coleman P J, Mercer S P, Schreier J D, Buser C A, Walsh E S, Hamilton K, Lobell R B, Tao W, Diehl R E, South V J, Davide J P, Kohl N E, Yan Y, Kuo L C, Li C, Fernandez-Metzler C, Mahan E A, Prueksaritanontd T and Hartmana G D, *Bioorg Med Chem Lett.,* 2007, **17(20),** 5677-5682.
22. Puig-Basagoiti F, Tilgner M, Forshey B M, Philpott S M, Espina N G, Wentworth D E, Goebel S J, Masters P S, Falgout B, Ren P, Ferguson D M and Shi P-Y, *Antimicrob Agents Chemother*., 2006, **50,** 1320-1329.
23. Ali M A, Shaharyar M, Siddiqui A A, Sriram D, Yogeeswari P and Clercq E D, *Acta Pol Pharma Drug Res*., 2007, **63,** 423-428.